

Specification

Retinoid action modifier.

The Field of Technology

This invention relates to a novel compound, and in fact relates to novel compound regulating physiological effect of intranuclear receptor-ligand represented by compounds (retinoid) having retinoic acid and retinoic acid-like physiological activities. The compound of this invention is useful, as effective ingredient of drug such as retinoid action modifier or the like.

Background Technique

Retinoic acid (vitamin A acid) is an active metabolite of vitamin A, and has extremely important physiological effects such as an action to differentiate premature cells in the middle of development into mature cells having specific functions, proliferation facilitation action, life maintenance action or the like of cells. Various kinds of vitamin A derivatives synthesised so far, for example, benzoic acid derivatives in accordance with Kokai 61-22047 and Kokai 61-76440, compounds in accordance with Journal of Medicinal Chemistry (1988, Vol. 81, No. 11, p.2182) have been elucidated to have similar physiological effects. The aforesaid compounds having retinoic acid and retinoic acid-like physiological activity are known generally, as "retinoid".

For example, it has been elucidated that all-trans retinoic acid binds, as ligand, to retinoic acid receptor (RAR) belonging to intranuclear receptor superfamily (Evans, R. M., Science, 240, p.889, 1988) existing within the cell nucleus, and controls proliferation • differentiation of animal cells or cell death or the like (Petkovich, M. et al., Nature, 330, pp. 444-450, 1987). It is suggested that the aforesaid compound having retinoic acid-like physiological activity (for example 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) carbamoyl] benzoic acid: Am80) binds to RAR in the same way as in retinoic acid, and displays the physiological activity (cf. Hashimoto, Y, Cell struct. Funct, 16, pp. 113-123, 1991, Hashimoto, Y, et al., Biochem. Biophys. Res. Commun. 166, pp. 1300-1307, 1990). These compounds have been found to be useful clinically for therapy or prevention of vitamin A deficiency, keratosis of an epithelial tissue, rheumatism, delayed type allergy, bone disease and leukemia and certain type of cancer.

A compound that acts antagonistically to such retinoid and decreases the aforesaid typical action of retinoid is known (Eyrolles, L, et al., Journal of Medicinal Chemistry, 37(10), pp. 1508-1517, 1994). On the other hand, there is hardly any report about substance that

reinforces the action of retinoid such as retinoic acid or the like even if it itself does not have retinoid action or has a very weak retinoid action. For example, in Kokai 8-59511, it is suggested that the compound which is a specific ligand with respect to RXR receptor has an action to reinforce the action of Am80 which is a specific ligand compound with respect to RAR- receptor. In this publication, it is suggested that 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl) carbonyl] benzoic acid-ethylene acetal reinforces the differentiation inducing action of the aforesaid Am80.

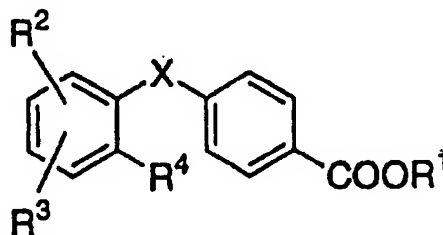
Moreover, these inventors found that benzodiazepine compounds such as 4-[5H-2,3-(2,5-dimethyl-2,5-hexano) -5-methyldibenzo[b,e][1,4]diazepin-11-yl] benzoic acid (HX600) or the like reinforced the action of retinoid (Umemiya et al., Chem. Pharm. Bull. 48, pp, 1827-1829, 1995). As for the action of this compound, it is thought as the activation of RXR receptors that form RXR-RAR heterodimer.

Disclosure of the Invention

The object of this invention is to put forward compounds having action to regulate the action of retinoid such as retinoic acid or the like. The object of this invention is to put forward compounds which can enhance the action of retinoid such as retinoic acid or the like even if it itself does not have retinoid action or has very weak retinoid action, or compounds which can suppress the action of retinoid.

In order to overcome these problems these inventors carried out assiduous investigations as a result discovered that compounds represented by the following general formula had an action to regulate the action of retinoid such as retinoic acid or the like. This invention was completed based on this discovery.

In other words, this invention puts forward compounds or salts thereof represented by the following general formula (1)



[wherein, R¹ denotes a hydrogen atom or C1-6 alkyl group; R², R³ and R⁴ each independently denote hydrogen atom, C1-6 alkoxy group or 1-6C alkyl group, or when R² and R³ are adjacent to each other, these are combined together with the carbon atoms on

the phenyl group to which R2 and R3 are bonded to form 5-6 membered ring (the aforesaid ring contains 1 or 2 or more 1-4C alkyl groups on the ring thereof, or a single condensed benzene ring optionally having 1 or 2 or more substituents); X denotes a divalent group represented by -C(R5)(R6)- or -NR7- (wherein, R5 denotes a hydrogen atom or hydroxy group, R6 denotes optionally substituted phenyl group or optionally substituted 5-6 membered saturated or unsaturated nitrogen-containing heterocyclic group, and R7 denotes a hydrogen atom, 1-12C alkyl group optionally having 1 or 2 or more unsaturated bonds, 3-12C cycloalkyl group, C4-12 cycloalkyl-substituted alkyl group, optionally substituted aralkyl group, 1-12C alkanoyl group, optionally substituted aroyl group or optionally substituted phenyl group)].

Moreover, from separate viewpoint, this invention puts forward a drug including, as an active ingredient, substance selected from the group comprising the aforesaid compound, pharmacologically acceptable salts thereof, hydrates thereof and solvate thereof. The drug of this invention can be used as retinoid action modifier or intranuclear receptor-ligand action modifier. Preferred forms of this invention put forward the aforesaid drug to be used as action modifier of the physiologically active substance which displays physiological effect by binding to intranuclear receptor belonging to intranuclear receptor superfamily; the aforesaid drug wherein the modifying action is action potentiation or action suppression; and also the aforesaid drug wherein the said physiologically active substance is retinoid.

Furthermore, in accordance with another viewpoint, this invention puts forward the use of the substance selected from the group comprising the aforesaid compound, pharmacologically acceptable salts thereof, hydrates thereof and solvate thereof for the production of the aforesaid drug, preferably a drug in a form of medicinal composition; and also a method of controlling the action of retinoid in vivo of mammals including human including a step to administer an effective quantity of the substance selected from the group comprising the aforesaid compound, pharmacologically acceptable salts thereof, hydrates thereof and solvate thereof to mammals including human. For example, this process can be used as preventive and/or therapeutic process of vitamin A deficiency; dermatosis such as keratosis of an epithelial tissue, psoriasis or the like; allergic diseases; immunologic disease such as rheumatism or the like; bone disease such as osteoporosis, fracture or the like; Alzheimer; Huntington's chorea; leukemia or cancer or the like, and can be used as prevention and/or therapeutic process of diseases such as diabetes mellitus, arteriosclerosis, hyperlipidemia, hypercholesterolemia, bone disease, rheumatism or immunologic disease or the like. Moreover, another form of this invention puts forward a

composition for drug including retinoid and a substance selected from the group comprising the aforesaid compound, pharmacologically acceptable salts thereof, hydrates thereof and solvate thereof.

Ideal form for Carrying Out the Invention

In compound represented by the aforesaid formula (1), R1 denotes a hydrogen atom or C1-6 alkyl group ("C1-6" denotes that the total number of carbon number contained in the group thereof is 1-6, and the other representations used in this specification are the same, too) alkyl group. The alkyl group may be either straight or branched chain, and for example, it is possible to use methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, tert-butyl group or the like. It is possible to use preferably methyl group, ethyl group or the like.

R2, R3 and R4 each independently denote hydrogen atom, C1-6 alkyl group, or 1-6C alkoxy group. The alkyl group may be either straight or branched chain, and for example, it is possible to use methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, tert-butyl group or the like. Among these, sterically bulky alkyl group, for example, isopropyl group, tert-butyl group or the like is preferably used. The 1-6C alkoxy group may be either straight or branched chain, and for example, it is possible to use methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, tert-butoxy group or the like. The sites of substitution of R2 and R3 are not restricted in particular, and it can be substituted each independently onto arbitrary positions, but preferably, they are substituted to the positions where R2 and R3 are adjacent to each other. For example, it is particularly preferred that R2 and R3 are respectively present at para position and meta position with respect to X.

When R2 and R3 are substituted onto positions adjacent to each other, they may form, together with carbon atoms on the phenyl group to which they are bonded, a five or six membered ring, preferably 6 membered ring. The 5-6 membered ring formed in this way may have 1 or 2 or more 1-4C alkyl groups on the ring thereof, and for example, may have 2-4 methyl groups and preferably 4 methyl groups. For example, 5,6,7,8-tetrahydronaphthalene ring and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene ring or the like is preferably formed by R2 and R3 and the benzene ring of the phenyl group to which R2 and R3 are substituted.

Moreover, the 5-6 membered ring, preferably benzene ring formed by R2 and R3 may contain a single condensed ring. In such case, 1 or 2 or more 1-4C alkyl groups may be

present on the 5-6 membered ring formed by the R2 and R3, and for example 2-4 methyl groups and preferably 4 methyl groups may be present on each of the rings. Moreover, condensed benzene ring may be unsubstituted, but may contain 1 or 2 or more substituents such as 1-6C alkyl group, 1-6C alkoxy group, halogen atom or the like. For example, 5,6,7,8-tetrahydroanthracenyl ring, 5,5,8,8-tetramethyl-5,6,7,8-tetrahydroanthracenyl ring or the like may be formed by benzene ring of the phenyl group on which R2 and R3 are substituted, R2 and R3, and the benzene ring to be condensed. The R4 is preferably hydrogen atom or C1-4 alkyl group.

X denotes a divalent group represented by -C(R5) (R6) - or -N(R7) -. R5 denotes a hydrogen atom or hydroxy group, but it is preferred to be hydrogen atom. R6 denotes optionally substituted phenyl group or optionally substituted 5-6 membered saturated or unsaturated nitrogen-containing heterocyclic group. When R6 denotes phenyl group containing substituent, the said phenyl group may contain 1 or 2 or more substituents. As substituent, for example, it is possible to use C1-6 alkyl group, 1-6C alkoxy group, hydroxy group, halogen atom, halogeno 1-6C alkyl group, carboxyl group, 1-6C alkoxycarbonyl group, C1-6 alkyl carbonyl group, substituted or unsubstituted amino group or the like, but 1-6C alkyl group, 1-6C alkoxy group or hydroxy group is preferred among these. Although the number and site of substitution of substituents on the said phenyl group are not restricted in particular, preferably, one substituent is present at p-position.

The 5-6 membered saturated or unsaturated nitrogen-containing heterocyclic group denoted by R6 contains at least one nitrogen atom as the atoms constituting the ring, and for example saturated nitrogen-containing heterocyclic group such as 1-pyrrolidinyl group, 1-piperidinyl group, morpholino group, 1-piperazinyl group or the like; unsaturated nitrogen-containing heterocyclic group such as 3-pyrrolin-1-yl group or the like; nitrogen containing heteroaryl group or the like such as 1-pyrrolyl group, 1-imidazolyl group, 1-pyrazolyl group, 1,2,4-triazol-1-yl group, 1-tetrazolyl group or the like. These nitrogen-containing heterocyclic groups may contain 1 or two or more heteroatoms other than nitrogen such as oxygen atom and sulfur atom. Moreover, the nitrogen-containing heterocyclic group may be unsubstituted, but may contain 1 or 2 or more substituents such as C1-6 alkyl group, 1-6C alkoxy group, hydroxy group, halogen atom, halogeno C1-6 alkyl group, carboxyl group, 1-6C alkoxycarbonyl group, 1-6C alkyl carbonyl group, substituted or unsubstituted amino group or the like. The bonding form between the nitrogen-containing heterocyclic group and the carbon atoms to which R5 and R6 were bonded is not limited in particular, however, the nitrogen atom

constituting the nitrogen-containing hetero ring is preferably bonded to the aforesaid carbon atom.

R7 denotes a hydrogen atom, 1-12C alkyl group optionally having 1 or 2 or more unsaturated bonds, 3-12C cycloalkyl group, 4-12C cycloalkyl-substituted alkyl group, optionally substituted aralkyl group, 1-12C alkanoyl group, optionally substituted aroyl group or optionally substituted phenyl group. The 1-12C alkyl group may be of branched chain or straight chain, and may contain 1 or 2 or more unsaturated bonds. As the unsaturated bond, 1 or 2 or more double bonds and 1 or 2 or more triple bonds may be combined. The double bond can be either Z-type or E-type. As 3-12C cycloalkyl group, it is possible to use for example cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group or the like, but these cycloalkyl groups may contain 1 or 2 or more alkyl groups on the ring thereof. As 4-12C cycloalkyl-substituted alkyl group, alkyl substituted with the aforesaid cycloalkyl group, preferably cycloalkyl-substituted C1-4 alkyl group, for example cyclopropylmethyl group or the like can be used.

As aralkyl group, for example, benzyl group, naphthylmethyl group, biphenyl methyl group, phenethyl group or the like may be proposed. As 1 or 2 or more substituents existing on the aryl ring of the substituted aralkyl group, for example, 1-6C alkyl group, C1-6 alkoxy group, hydroxy group, halogen atom, halogenation 1-6C alkyl group, carboxyl group, C1-6 alkoxy carbonyl group, 1-6C alkyl carbonyl group, substituted or unsubstituted amino group or the like can be used.

As 1-12C alkanoyl group, for example, acetyl group, propanoyl group, butanoyl group or the like can be used, and as aroyl group, for example benzoyl group, naphthoyl group or the like can be used. As 1 or 2 or more substituents existing on the aryl ring of the substituted aroyl group, for example, C1-6 alkyl group, 1-6C alkoxy group, hydroxy group, halogen atom, halogeno 1-6C alkyl group, carboxyl group, C1-6 alkoxy carbonyl group, C1-6 alkyl carbonyl group, substituted or unsubstituted amino group or the like can be used. The 1 or 2 or more substituents of the substituted phenyl group can be chosen among the aforesaid substituents.

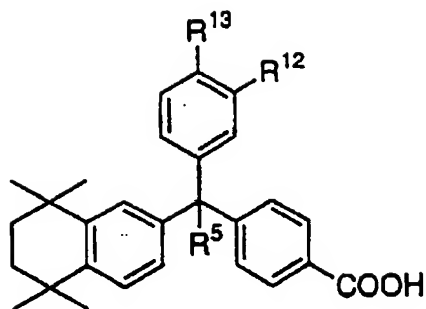
When R7 denotes substituted phenyl group, a phenyl group containing two C1-6 alkyl groups on adjacent positions is ideal, and the two adjacent 1-6C alkyl groups may be combined to each other to form five or six membered ring, preferably 6 membered ring. The ring formed in this way may contain further 1 or 2 or more 1-4C alkyl groups on the ring thereof, preferably 2-4 methyl groups, more preferably 4 methyl groups. For

example, as R7, 5,6,7,8-tetrahydronaphthalen-2-yl group, 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl group or the like can be used.

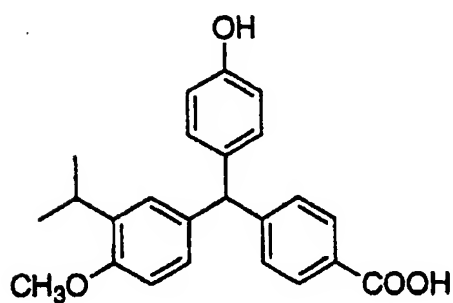
Acid addition salt or base addition salt is included in the compounds of this invention. As acid addition salt, mineral acid salt such as hydrochloride or hydrobromide or the like, or organic salt such as p-toluenesulfonate, methanesulfonate, oxalate, tartrate or the like can be nominated. As base addition salt, for example, metal salt such as sodium salt, potassium salt, magnesium salt or calcium salt or the like, organic amine salt or the like such as ammonium salt or ethanolamine salt or the like or triethylamine salt can be used.

There are cases that the compounds of this invention have 1 or 2 or more asymmetric carbons, and arbitrary optical isomer on the basis of such asymmetric carbon, arbitrary mixture of optical isomer, racemic body, diastereoisomer on the basis of asymmetric two or more carbons, arbitrary mixture or the like of diastereoisomer are all included in the scope of this invention. Moreover, arbitrary geometrical isomers on the basis of 1 or 2 or more double bonds are included. Moreover, arbitrary hydrate or solvate of free compound or compound in a form of salt are also included.

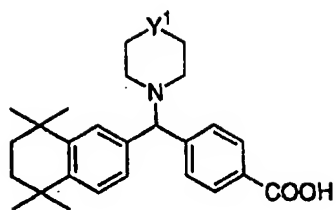
Among the compounds of this invention represented by the aforesaid general formula (1), preferred compounds are shown, but the compounds of this invention are not restricted to the following compounds.



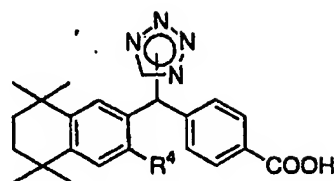
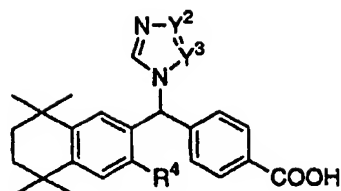
	R ⁵	R ¹²	R ¹³
DM010	H	H	H
DM011	H	H	OH
DM012	OH	H	H
DM013	H	H	OCH ₃
DM014	H	H	N(CH ₃) ₂
DM015	H	-OCH ₂ CH ₂ O-	
DM016	H	H	OCH ₂ CH ₂ -N



DM040

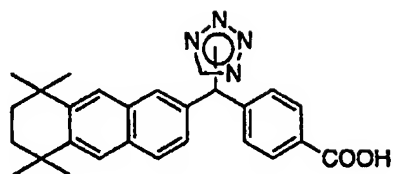


	Y ¹
DM020	CH ₂
DM021	O
DM022	NCH ₃

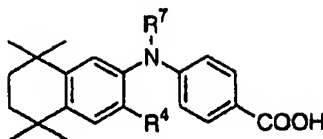


	R ⁴	Y ²	Y ³
DM030	H	C	N
DM032	H	C	C
DM130	CH ₃	C	N

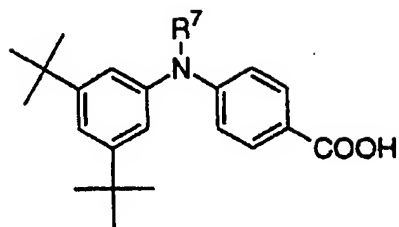
DM031 (TLC low polarity isomer)
DM036 (TLC high polarity isomer)



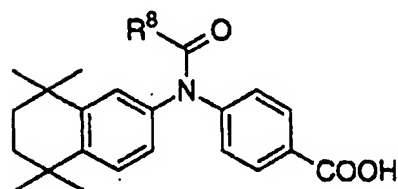
DM033 (TLC low polarity isomer)



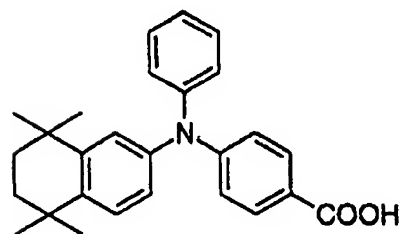
	R ⁴	R ⁷		R ⁴	R ⁷
DA010	H	H	DA040	H	CH ₂ C ₆ H ₅
DA011	H	CH ₃	DA041	H	CH ₂ C ₆ H ₄ - <i>p</i> -CH ₃
DA012	H	C ₂ H ₅	DA042	H	CH ₂ C ₆ H ₄ - <i>p</i> -CF ₃
DA013	H	<i>n</i> -C ₃ H ₇	DA045	H	CH ₂ C ₆ H ₄ - <i>p</i> -OC ₂ H ₅
DA014	H	<i>n</i> -C ₄ H ₉	DA046	H	CH ₂ C ₆ H ₄ - <i>o</i> -C ₆ H ₅
DA015	H	<i>n</i> -C ₅ H ₁₁	DA048	H	CH ₂ -2-C ₁₀ H ₇
DA016	H	<i>n</i> -C ₆ H ₁₃	DA112	CH ₃	C ₂ H ₅
DA017	H	<i>n</i> -C ₇ H ₁₅	DA113	CH ₃	<i>n</i> -C ₃ H ₇
DA018	H	<i>n</i> -C ₈ H ₁₇	DA114	CH ₃	<i>n</i> -C ₄ H ₉
DA020	H	CH ₂ C≡CH	DA120	CH ₃	CH ₂ C≡CH
DA021	H	CH ₂ CH=CH ₂	DA121	CH ₃	CH ₂ CH=CH ₂
DA022	H	<i>iso</i> -C ₃ H ₇	DA122	CH ₃	<i>iso</i> -C ₃ H ₇
DA023	H	<i>c</i> -C ₃ H ₅	DA123	CH ₃	<i>c</i> -C ₃ H ₇
DA024	H	CH ₂ (<i>c</i> -C ₃ H ₅)	DA124	CH ₃	CH ₂ (<i>c</i> -C ₃ H ₅)
DA025	H	CH ₂ CH(CH ₃) ₂	DA125	CH ₃	CH ₂ CH(CH ₃) ₂
DA028	H	CH ₂ CH=C(CH ₃) ₂	DA130	CH ₃	CH ₂ (<i>c</i> -C ₄ H ₇)
DA030	H	CH ₂ (<i>c</i> -C ₄ H ₇)	DA162	<i>n</i> -C ₃ H ₇	C ₂ H ₅
DA036	H	CH ₂ (<i>c</i> -C ₆ H ₁₁)	DA163	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇



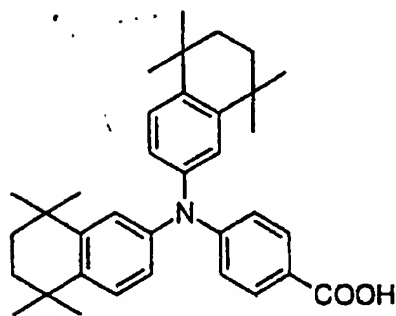
	R ⁷
DA212	C ₂ H ₅
DA213	<i>n</i> -C ₃ H ₇
DA222	<i>iso</i> -C ₃ H ₇
DA223	<i>c</i> -C ₃ H ₅
DA224	CH ₂ (<i>c</i> -C ₃ H ₅)
DA230	CH ₂ (<i>c</i> -C ₄ H ₇)



	R ⁸
DA051	CH ₃
DA055	C ₆ H ₅
DA058	C ₆ H ₄ - <i>p</i> -COOH



TA001



TA012

In examples of this specification, processes for the production of the said preferred compounds included in formula (1) of this invention are described in greater detail. Accordingly, compounds included in the scope of this invention can be produced in each case by suitably modifying or altering the starting materials, reaction conditions and reagents or the like used in these processes for the production. Wherein, the process for the production of the compound of this invention is not restricted to the processes described in greater detail in the Examples.

The compounds of this invention represented by the aforesaid formula (1) have an action to regulate physiological effect of retinoid. In this specification, the term "control action" or a similar word thereof need to be interpreted in the widest sense including the potentiation or inhibition of the action. Whether the compound of this invention has

which of the potentiation action or inhibitory action can be easily determined by the method shown in the Test Examples of this specification.

Among the compounds of this invention represented by the aforesaid formula (I), the retinoid action potentiating compounds have characteristics that they themselves do not substantially have retinoid-like action or have weak or moderate retinoid-like action, however, when the compounds of this invention are placed in the co-presence of retinoid such as retinoic acid or the like, the physiological activity of retinoid (as typical example, cell differentiation action, cell proliferation promoting action and life maintenance action or the like) can be markedly enhanced. No specific theory is adhered to, but when the compound of this invention itself has retinoid action, the action thereof is synergistic action.

Accordingly, when retinoid including retinoic acid or compounds having retinoic acid-like biological action (for example 4-[[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] carbamoyl] benzoic acid: Am80 or the like) is administered as a drug for prevention and/or therapy of diseases as vitamin A deficiency, dermatosis such as keratosis of an epithelial tissue, psoriasis or the like, allergic disease, immunologic disease such as rheumatism or the like, bone disease such as osteoporosis, fracture or the like, Alzheimer; Huntington's chorea, leukaemia, cancer or the like, the compounds of this invention can be used as the action potentiation agent of the said retinoid.

Moreover, even when the retinoid is not administered for the prevention and/or therapy of aforesaid diseases, the compounds of this invention enhance the action of retinoic acid already present in vivo, therefore, the compound of this invention themselves can be administered for the purpose of prevention and/or therapy of aforesaid diseases. Moreover, the compounds of this invention can be used for action potentiation of physiologically active substances that displays physiological action by binding as ligands to receptors belonging to intranuclear receptor superfamily present within the cell nucleus (Evans, R.M, Science, 240, p.889, 1988), for example, steroidal compound, vitamin D compound such as vitamin D3 or the like or thyroxine or the like. For example, it is also useful as preventive and/or therapeutic agent of diseases such as diabetes mellitus, arteriosclerosis, hyperlipidemia, hypercholesterolemia, bone disease, rheumatism, immunologic disease or the like. Wherein the applications of the compounds of this invention are not restricted to the applications described as above.

Moreover, among the compounds of this invention represented by the aforesaid formula (1), the retinoid action inhibitory compounds have action to markedly inhibit the physiological effect of retinoid (as typical example, cell differentiation action, cell proliferation promoting action and life maintenance action or the like). Moreover, the aforesaid compounds can inhibit the actions of substances that displays physiological action by binding to receptors belonging to intranuclear receptor superfamily present within the cell nucleus, for example, steroidal compound, vitamin D compound such as vitamin D3 or the like or thyroxine, or the action of orphan receptors with unknown ligands or the like. Accordingly, the retinoid action inhibitory compounds can be used, for example, for the control of action expression of these physiologically active substances, and can be used for prevention and/or therapy of diseases due to aberration of biological actions involving one or two or more intranuclear receptors belonging to intranuclear receptor superfamily.

When the compounds of this invention are used as drugs, one or more substances selected from the compound of the said general formula (1), pharmacologically acceptable salts thereof, and hydrates thereof and solvate thereof may be administered as they are, but, preferably, a medicinal composition for oral or parenteral use containing the aforesaid one or more substances as effective component is produced using the formulation additives available to a person skilled in the art, and can be administered. Moreover, one or more of the aforesaid substances are formulated in the drug containing retinoid such as retinoic acid or the like as an effective component, and this can be used as a medicinal composition in a form of combined agent.

As medicinal composition suitable for oral administration, for example, tablet, encapsulated formulation, powder, fine granule, granule, liquid agent, and syrup or the like can be nominated, and medicinal composition suitable for parenteral administration, for example injection, drip infusion agent, suppository, inhalant, instillation, nasal drops, ointment, cream agent, and patch or the like are nominated. As pharmacologically and pharmaceutically acceptable formulation additives to be used for the production of the aforesaid medicinal composition, for example, excipient, disintegrating agent or disintegration aid, binding agent, lubricant, coating agent, dye, diluent, base, solvent or solubilizer, isotonic agent, pH modifier, stabilising agent, propellant, and binder or the like can be nominated.

The dose of the drug of this invention is not limited in particular, and suitable dosage can be easily selected in any administration method when the action of retinoid is controlled

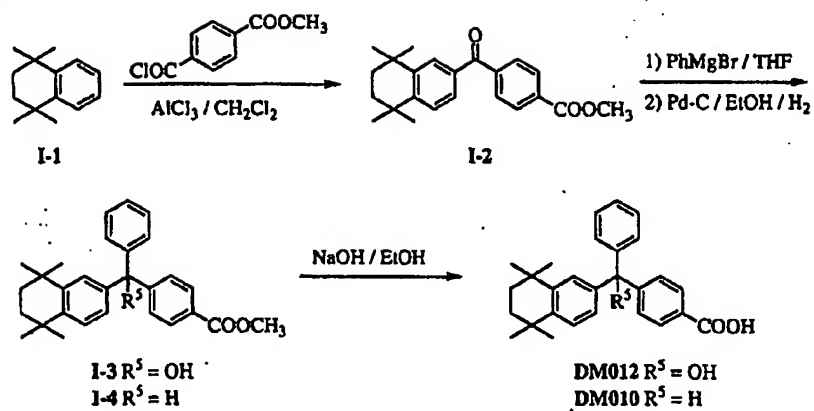
by combining the drug of this invention with the drug containing retinoid such as retinoic acid or the like as effective component, or when the drug of this invention is administered for the action control of retinoic acid already present in vivo without combining the drug containing retinoid. For example, in the case of oral administration, it can be used in a range of 0.01-1,000 mg per day for adult. When the drug of this invention is co-used with the drug containing retinoid as effective component, the drug of this invention can be administration.

Examples

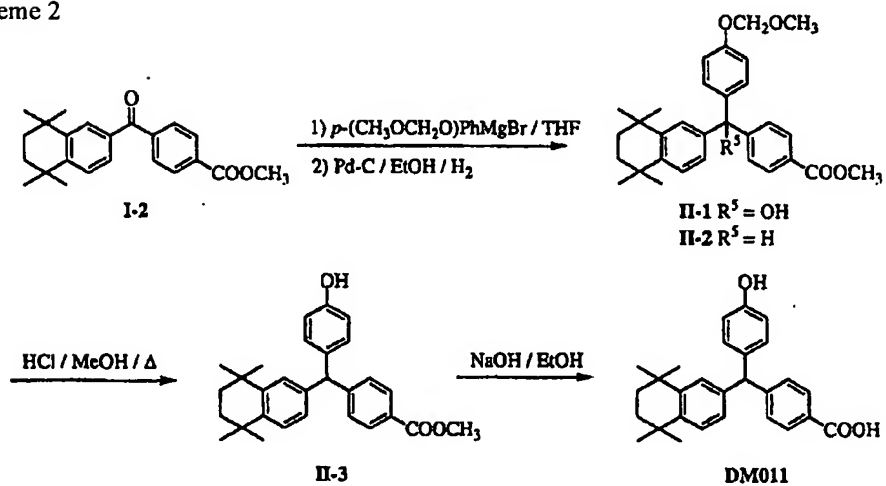
Hereinafter, this invention will be described in greater detail using Examples furthermore. However, the range of the invention is not restricted to the range of the following Examples.

A process for the production adopted with the following Examples is shown in Schemes 1-8. Compound numbers in Schemes correspond with compound numbers of the said preferred compounds and compound numbers in Examples.

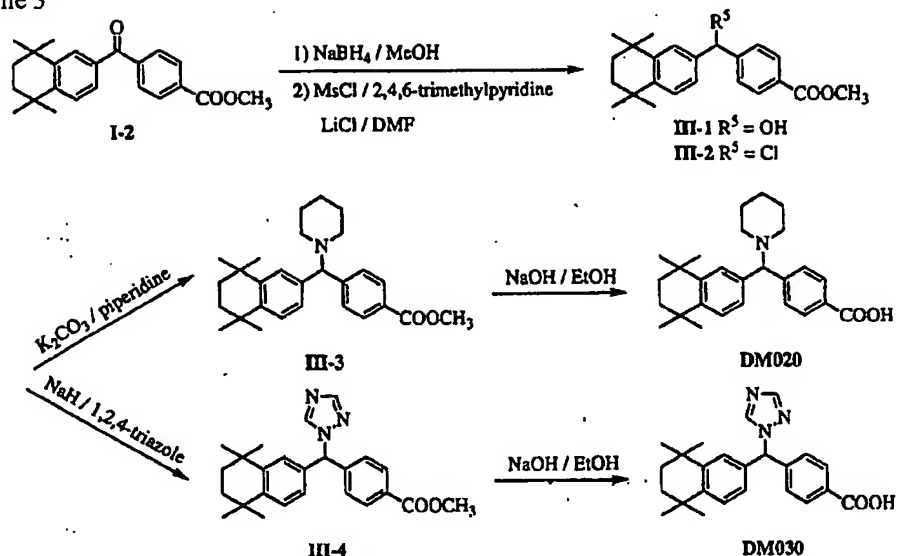
Scheme 1



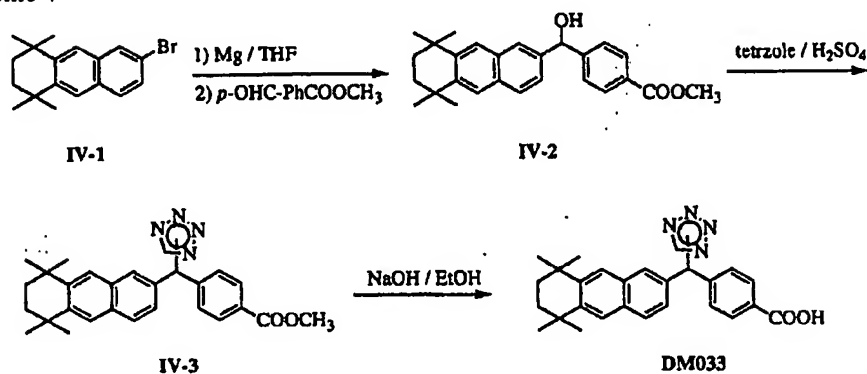
Scheme 2



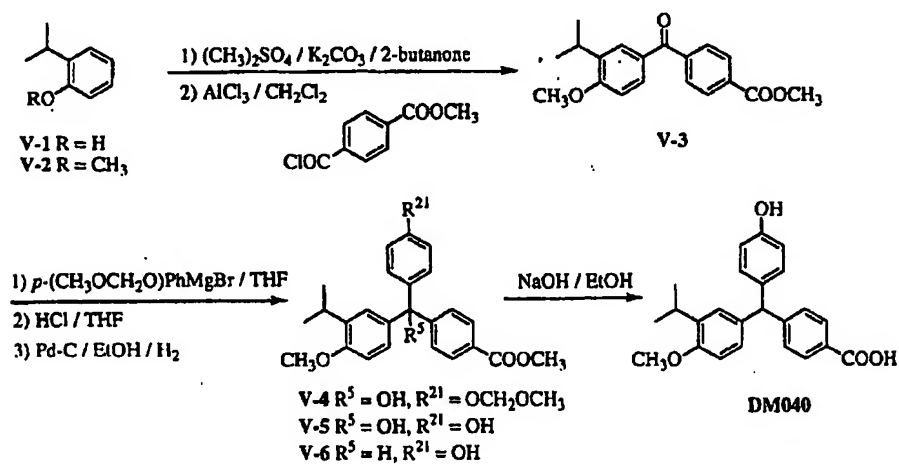
Scheme 3



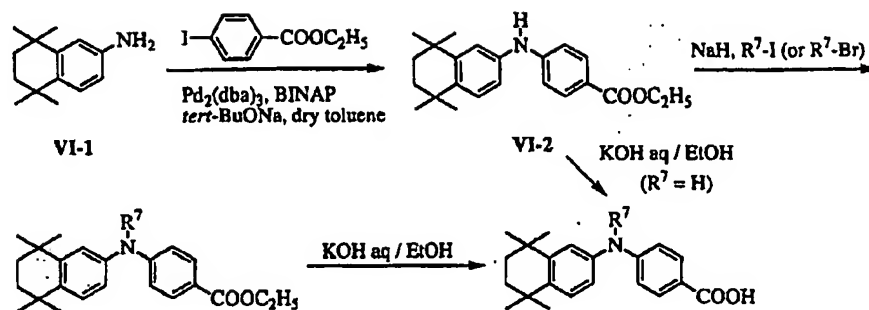
Scheme 4



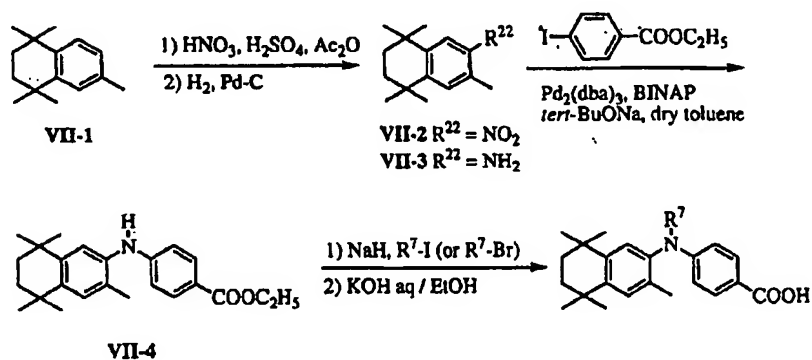
Scheme 5



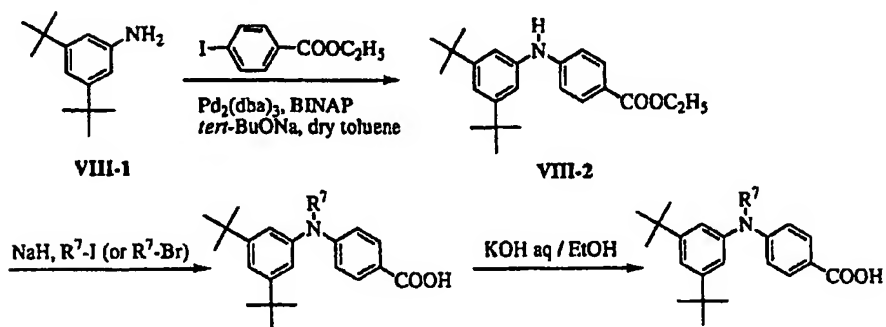
Scheme 6



Scheme 7



Scheme 8



Example 1

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) phenylmethyl] benzoic acid (DMO10) (Scheme 1)

To methylene chloride solution (100 ml) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (I-1, 10.0 g) and monomethyl terephthalic acid chloride (10.0 g), aluminum chloride (14.3 g) was added at room temperature slowly, and thereafter, the mixture was stirred at room temperature for three hours. The reaction mixture was discharged into hydrochloric acid aqueous solution including ice and extraction was carried out with chloroform. The solvent was eliminated by distillation under reduced pressure and the residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1) and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) carbonyl] methyl benzoate (Compound I-2, 11.2 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.15 (2H, d, J = 8 Hz), 7.83 (2H, d, J = 8 Hz), 7.79 (1H, d, J = 2 Hz), 7.54 (1H, dd, J = 8, 2 Hz), 7.41 (1H, d, J = 8 Hz), 3.95 (3H, s), 1.73 (4H, s), 1.32 (6H, s), 1.29 (6H, s).

Anhydrous THF solution (30 ml) of Compound I-2 (4.99 g) was cooled to 0°C under nitrogen atmosphere and Grignard solution (1M THF solution, 14.3 ml) of the bromobenzene was slowly added dropwise. The ice bath was taken off and the mixture was stirred at room temperature for 40 minutes, and the reaction solution was discharged into iced water and extraction was carried out with ethyl acetate. The solvent was eliminated by distillation under reduced pressure, and thereafter the residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) and 4-[phenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) hydroxyl methyl] methyl benzoate (I-3, 4.45 g) was obtained.

¹H-NMR (90 MHz, CDCl₃) 7.96 (2H, d, J = 8 Hz), 7.42 (2H, d, J = 8 Hz), 7.37-6.81 (8H, m), 3.89 (3H, s), 2.85 (1H, s), 1.66 (4H, s), 1.27 (6H, s), 1.14 (6H, s).

Pd-C (0.5 g) was added to Compound I-3 (4.0 g) dissolved in ethanol (220 ml) and the mixture was stirred at room temperature for 46 hours under hydrogen atmosphere. The reaction liquor was filtered by passing through celite, and thereafter the solvent was eliminated by distillation under reduced pressure. The obtained residue was recrystallised with light petroleum, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) phenylmethyl] methyl benzoate (I-4, 1.47 g) was obtained.

¹H-NMR (90 MHz, CDCl₃) 7.94 (2H, d, J = 8 Hz), 7.44-6.69 (10H, m), 5.51 (1H, s), 3.89 (3H, s), 1.66 (4H, s), 1.26 (6H, s), 1.16 (6H, s).

To Compound I-4 (1.30 g) dissolved in ethanol (60 ml), 3.5 M sodium hydroxide aqueous solution (4.5 ml) was added, and the mixture was stirred at 60°C for one hour 30 minutes. The reaction liquor was concentrated under reduced pressure, and water was added to the residue, and the mixture was acidified with 6 N hydrochloric acid while cooling to 0°C. The precipitated crystals were separated by filtration, and after drying, were washed with light petroleum, and DMO10 (0.59 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.98 (2H, d, J = 8 Hz), 7.30-7.16 (6H, m), 7.09 (2H, d, J = 7 Hz), 7.01 (1H, d, J = 2 Hz), 6.79 (1H, dd, J = 8, 2 Hz), 5.50 (1H, s), 1.65 (4H, s), 1.25 (6H, s), 1.16 (6H, s).

Example 2

Production of 4-[4-hydroxyphenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) methyl] benzoic acid (DMO11) (Scheme 2)

To anhydrous THF solution (50 ml) of Compound I-2 (8.10 g), Grignard solution (THF, 20 ml) of 1-bromo-4-methoxymethoxy benzene (5.0 g) prepared separately was slowly added dropwise under cooling, and thereafter, the mixture was stirred at room temperature for two hours. The reaction solution was discharged into iced water and extraction was carried out with ethyl acetate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified using silica gel chromatography (n-hexane : ethyl acetate = 3 : 1) and Compound II-1 (7.50 g) was obtained.

¹H-NMR (90 MHz, CDCl₃) 7.97 (2H, d, J = 8 Hz), 7.40 (2H, d, J = 8 Hz), 7.3-6.8 (7H, m), 5.18 (2H, s), 3.90 (3H, s), 3.47 (3H, s), 2.75 (1H, s), 1.69 (4H, s), 1.25 (6H, s), 1.15 (6H, s).

Pd-C (0.45 g) was added to Compound II-1 (1.81 g) dissolved in ethanol (100 ml) and the mixture was stirred at room temperature for eight hours 30 minutes under hydrogen atmosphere. The reaction solution was filtered by passing through celite, and thereafter the solvent was eliminated by distillation under reduced pressure, and Compound II-2 (0.76 g) was obtained.

¹H-NMR (90 MHz, CDCl₃) 7.93 (2H, d, J = 8 Hz), 7.53-6.69 (7H, m), 7.18 (2H, d, J = 8 Hz), 5.46 (1H, s), 5.15 (2H, s), 3.89 (3H, s), 3.47 (3H, s), 1.66 (4H, s), 1.26 (6H, s), 1.16 (6H, s).

To Compound II-2 (0.75 g) dissolved in methanol (60 ml), two drops of concentrated hydrochloric acid were added and it was heated to 40-50°C and was stirred for nine hours 30 minutes. The reaction solution was concentrated under reduced pressure, and the

residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1) and Compound II-3 (0.63 g) was obtained.

¹H-NMR (90 MHz, CDCl₃) 7.93 (2H, d, J = 8 Hz), 7.37-6.62 (9H, m), 5.44 (1H, s), 5.20 (1H, br s), 3.89 (3H, s), 1.65 (4H, s), 1.25 (6H, s), 1.16 (6H, s).

To Compound II-3 (0.60 g) dissolved in ethanol (10 ml), 2.7 N sodium hydroxide aqueous solution (2 ml) was added, and the mixture was stirred at 60°C for two hours. The reaction solution was concentrated under reduced pressure, and water was added to the residue, and 6 N hydrochloric acid was added while cooling to 0°C and the mixture was acidified. The precipitated crystals were separated by filtration and were well washed with water and thereafter, were dried under reduced pressure. This crystals were recrystallised from diethyl ether-light petroleum and DMO11(0.40 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.01 (2H, d, J = 8 Hz), 7.22 (2H, d, J = 8 Hz), 7.19(1H, d, J = 8 Hz), 7.00 (1H, d, J = 2 Hz), 6.97 (2H, d, J = 8 Hz), 6.79 (1H, dd, J = 8, 2 Hz), 6.76 (2H, d, J = 8 Hz), 5.46 (1H, s), 1.66 (4H, s), 1.23 (6H, s), 1.16 (6H, s).

Example 3

Production of 4-[phenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)hydroxymethyl] benzoic acid (DMO12) (Scheme 1)

In Compound I-3 (2.0 g) dissolved in ethanol (30 ml), aqueous solution (5 ml) of sodium hydroxide (0.60 g) was added and the mixture was stirred at about 50°C for three hours. The reaction liquor was concentrated under reduced pressure, and water was added to the residue, and the mixture was acidified with hydrochloric acid aqueous solution. The precipitated crystals were separated by filtration, and after drying, were washed with light petroleum, and DMO12 (1.2 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, d, J = 8 Hz), 7.38-7.20 (8H, m), 7.15 (1H, d, J = 2 Hz), 6.89 (1H, d, J = 8, 2 Hz), 6.46 (1H, s), 1.65 (4H, s), 1.22 (6H, s), 1.10 (6H, s).

Example 4

Production of 4-[4-methoxyphenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) methyl] benzoic acid (DMO13)

Compound I-2 (reference Example 1) and p-bromo anisole were as the starting material, and according to the process in accordance with Example 1, DMO13 was obtained.

¹H-NMR (400 MHz, CDCl₃) 12.82 (1H, br s), 7.87 (2H, d, J = 8 Hz), 7.24-7.18 (3H, m), 7.07 (1H, s), 7.03 (2H, d, J = 8 Hz), 6.88 (2H, d, J = 8 Hz), 6.83 (1H, d, J = 8 Hz), 5.54 (1H, s), 3.72 (3H, s), 1.61 (4H, s), 1.21 (6H, s), 1.14 (3H, s), 1.13 (3H, s).

Example 5

Production of 4-[4-dimethylaminophenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) methyl] benzoic acid (DMO14)

Compound I-2 and 4-bromo-N,N-dimethylaniline were used as the starting material, and, according to the process in accordance with Example 1, DMO14 was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.00 (2H, d, J = 8 Hz), 7.24 (2H, d, J = 8 Hz), 7.18 (1H, d, J = 8 Hz), 7.03 (1H, d, J = 2 Hz), 6.97 (2H, d, J = 9 Hz), 6.81 (1H, dd, J = 8, 2 Hz), 6.68 (2H, d, J = 9 Hz), 5.43 (1H, s), 2.92 (6H, s), 1.65 (4H, s), 1.25 (6H, s), 1.17 (3H, s), 1.16 (3H, s).

Example 6

Production of 4-[3,4-methylenedioxyphenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) methyl] benzoic acid (DMO15)

Compound I-2 and 4-bromo-1,2-(methylene dioxy) benzene were as the starting material, and, according to the process in accordance with Example 1, DMO15 was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.01 (2H, d, J = 8 Hz), 7.23 (2H, d, J = 8 Hz), 7.20 (1H, d, J = 8 Hz), 7.01 (1H, d, J = 2 Hz), 6.80 (1H, dd, J = 8, 2 Hz), 6.73 (1H, d, J = 8 Hz), 6.59 (1H, d, J = 2 Hz), 6.57 (1H, dd, J = 8, 2 Hz), 5.93 (2H, s), 5.44 (1H, s), 1.66 (4H, s), 1.26 (6H, s), 1.18 (3H, s), 1.17 (3H, s).

Example 7

Production of 4-[4-[2-(1-pyrrolidinyl) ethoxy] phenyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) methyl] benzoic acid (DMO16)

Compound I-2 1-[2-(4-bromo phenoxy) ethyl] pyrrolidine were used as the starting material, and DMO16 was obtained according to the process in accordance with Example 1.

¹H-NMR (400 MHz, CDCl₃+DMSO-d₆) 12.28 (1H, br s), 7.94 (2H, d, J = 8 Hz), 7.18 (1H, d, J = 8 Hz), 7.17 (2H, d, J = 8 Hz), 7.03 (2H, d, J = 9 Hz), 7.01 (1H, d, J = 2 Hz), 6.85 (2H, d, J = 9 Hz), 6.78 (1H, dd, J = 8, 2 Hz), 5.45 (1H, s), 4.48 (2H, t, J = 5 Hz), 3.76 (2H, br s), 3.54 (1H, t, J = 5 Hz), 3.11 (2H, br s), 2.14 (4H, br s), 1.66 (4H, s), 1.25 (6H, s), 1.17 (3H, s), 1.16 (3H, s).

Example 8

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene 2-yl) piperidinomethyl] benzoic acid (DMO20) (Scheme 3)

To Compound I-2 (5.0 g) dissolved in methanol (200 ml), sodium borohydride (0.60 g) was added slowly at room temperature, and thereafter, the mixture was further stirred for

two hours. The reaction mixture was discharged into iced water, and the precipitated crystals were separated by filtration, and were thoroughly washed with water, and Compound III-1 (5.10 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.90 (2H, d, J = 8 Hz), 7.47 (2H, d, J = 8 Hz), 7.29 (1H, d, J = 2 Hz), 7.25 (1H, d, J = 8 Hz), 7.04 (1H, dd, J = 8, 2 Hz), 5.82 (1H, d, J = 3 Hz), 3.89 (3H, s), 2.34 (1H, d, J = 3 Hz), 1.66 (4H, s), 1.28-1.26 (12H, m).

In anhydrous dimethylformamide (DMF) solution (30 ml) of Compound III-1 (5.10 g), 2,4,6-trimethylpyridine (2.1 g) and lithium chloride (0.74 g), methane sulphonyl chloride (2.0 g) was added at room temperature slowly, and thereafter, the reaction mixture was gradually heated and stirred at about 50°C for three hours. The reaction mixture was discharged into iced water and extraction was carried out with ethyl acetate, and thereafter the organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1) and Compound III-2 (2.4 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.02 (2H, d, J = 8 Hz), 7.51 (2H, d, J = 8 Hz), 7.30 (1H, d, J = 2 Hz), 7.26 (1H, d, J = 8 Hz), 7.09 (1H, dd, J = 8, 2 Hz), 6.11 (1H, s), 3.91 (3H, s), 1.67 (4H, s), 1.26 (6H, s), 1.23 (6H, s).

Anhydrous DMF solution (10 ml) of Compound III-2 (1.001 g), piperidine (0.691 g) and potassium carbonate (1.175 g) was stirred at about 90°C for three hours. The reaction solution was cooled, and was discharged into iced water, and extraction was carried out with ethyl acetate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 8 : 1) and Compound III-3 (0.844 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.93 (2H, d, J = 8 Hz), 7.48 (2H, d, J = 8 Hz), 7.28 (1H, d, J = 2 Hz), 7.14 (1H, d, J = 8 Hz), 7.03 (1H, dd, J = 8, 2 Hz), 4.21 (1H, s), 3.87 (3H, s), 2.23 (4H, m), 1.62 (4H, s), 1.55 (4H, m), 1.42 (2H, m), 1.23 (6H, s), 1.21 (6H, s).

5 N sodium hydroxide aqueous solution (1.2 ml) was added to the aforesaid ester (0.844 g) dissolved in ethanol (10 ml) and the mixture was stirred at 50°C for one hour. The reaction mixture was concentrated under reduced pressure, and water was added to the residue and the mixture was neutralized with hydrochloric acid aqueous solution while cooling to 0°C. Extraction of the mixture was carried out with ethyl acetate, and the organic phase was concentrated under reduced pressure, and the obtained residue was recrystallized with light petroleum, and DMO20 (0.756 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.08 (2H, d, J = 8 Hz), 7.64 (2H, d, J = 8 Hz), 7.40 (1H, d, J = 2 Hz), 7.20 (1H, dd, J = 8, 2 Hz), 7.17 (1H, d, J = 8 Hz), 4.47 (1H, s), 2.59 (4H, m), 1.70 (4H, m), 1.61 (4H, s), 1.48 (2H, m), 1.21 (6H, s), 1.19 (6H, s).

Example 9

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)morpholinomethyl] benzoic acid (DMO21)

Compound III-2 and morpholine were used as the starting materials, and DMO21 was obtained according to the process in accordance with Example 8.

¹H-NMR (400 MHz, CDCl₃) 8.01 (2H, d, J = 8 Hz), 7.55 (2H, d, J = 8 Hz), 7.30 (1H, d, J = 2 Hz), 7.17 (1H, d, J = 8 Hz), 7.08 (1H, dd, J = 8, 2 Hz), 4.22 (1H, s), 3.72 (4H, m), 2.38 (4H, m), 1.62 (4H, s), 1.24 (3H, s), 1.23 (3H, s), 1.21 (6H, s).

Example 10

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-(4-methylpiperazine-1-yl)methyl] benzoic acid (DMO22)

Compound III-2 and 1-methylpiperazine were as the starting material. According to the process in accordance with Example 8, DMO22 was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.92 (2H, d, J = 8 Hz), 7.37 (2H, d, J = 8 Hz), 7.27 (1H, d, J = 1.5 Hz), 7.15 (1H, d, J = 8 Hz), 7.08 (1H, dd, J = 8, 1.5 Hz), 4.32 (1H, s), 2.87 (4H, br s), 2.55 (4H, br s), 2.52 (3H, s), 1.62 (4H, s), 1.21 (12H, s).

Example 11

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-(1,2,4-triazole-1-yl)methyl] benzoic acid (DMO30) (Scheme 3)

1,2,4-triazole (0.17 g) was added to anhydrous DMF solution (20 ml) of sodium hydride (60 % in oil, 0.11 g) at room temperature under dried nitrogen atmosphere and the mixture was stirred for about one hour, and thereafter, Compound III-2 (1.0 g) was added. This reaction liquor was gradually heated and was stirred at about 80°C for five hours. The reaction mixture was cooled, and was discharged into iced water and extraction was carried out with ethyl acetate. The organic phase was concentrated under reduced pressure, and the residue was purified using silica gel column chromatography (ethyl acetate) and Compound III-4 (0.81 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.05 (2H, d, J = 8 Hz), 8.04 (1H, s), 7.92 (1H, s), 7.28 (1H, d, J = 8 Hz), 7.18 (2H, d, J = 8 Hz), 7.10 (1H, d, J = 2 Hz), 6.90 (1H, dd, J = 8, 2 Hz), 6.73 (1H, s), 3.92 (3H, s), 1.67 (4H, s), 1.26 (6H, s), 1.20 (3H, s), 1.17 (3H, s).

Aqueous solution (3 ml) of sodium hydroxide (0.24 g) was added to Compound III-4 (0.80 g) dissolved in ethanol (10 ml) and this mixture was stirred at about 50°C for three hours. The reaction solution was concentrated under reduced pressure, and water was added to the residue, and the mixture was adjusted to pH 6 with hydrochloric acid aqueous solution, thereafter, extraction of the mixture was carried out with ethyl acetate. The organic phase was concentrated under reduced pressure, and the residue was washed with light petroleum, and DMO30 (0.53 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.09 (2H, d, J = 8 Hz), 8.07 (1H, s), 7.98 (1H, s), 7.30 (1H, d, J = 8 Hz), 7.19 (2H, d, J = 8 Hz), 7.12 (1H, d, J = 2 Hz), 6.89 (1H, d, J = 8, 2 Hz), 6.75 (1H, s), 1.68 (4H, s), 1.27 (3H, s), 1.26 (3H, s), 1.21 (3H, s), 1.17 (3H, s).

Example 12

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-tetrazoymethyl] benzoic acid (DMO31 and DMO36)

1H-tetrazole (1.87 g) and five drops of concentrated sulfuric acid were added to acetic acid suspension (50 ml) of Compound III-1 (3.0 g), and the mixture was stirred at room temperature for 24 hours. The reaction liquor was discharged into iced water, and it was neutralized with sodium hydroxide aqueous solution and extraction was carried out with ethyl acetate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified using silica gel column chromatography (n-hexane : chloroform = 1 : 1 and thereafter 0 : 1) and two kinds of isomer (TLC low polarity ester 0.810 g and TLC high polarity ester 1.50 g) of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-tetrazoymethyl] methyl benzoate were obtained.

Low polarity ester

¹H-NMR (400 MHz, CDCl₃) 8.57 (1H, s), 8.03 (2H, d, J = 8 Hz), 7.31 (2H, d, J = 8 Hz), 7.31 (1H, s), 7.29 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 2 Hz), 7.01 (1H, dd, J = 8, 2 Hz), 3.91 (3H, s), 1.66 (4H, s), 1.25 (6H, s), 1.19 (3H, s), 1.18 (3H, s).

High polarity ester

¹H-NMR (400 MHz, CDCl₃) 8.44 (1H, s), 8.06 (2H, d, J = 8.5 Hz), 7.32 (1H, d, J = 8 Hz), 7.15 (2H, d, J = 8 Hz), 7.10 (1H, d, J = 2 Hz), 7.05 (1H, s), 6.87 (1H, dd, J = 8, 2 Hz), 3.93 (3H, s), 1.68 (4H, s), 1.27 (6H, s), 1.21 (3H, s), 1.16 (3H, s).

5N sodium hydroxide aqueous solution (1 ml) was added to the aforesaid low polarity ester (0.622 g) dissolved in ethanol (10 ml) and the mixture was stirred at 50°C for three hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, and hydrochloric acid aqueous solution was added while cooling to 0°C, and the mixture was made acidic. Extraction of this mixture was carried out with ethyl acetate, and the organic phase was concentrated under reduced pressure, and the obtained residue was recrystallised with light petroleum, and DMO31 (0.226 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.59 (1H, s), 8.10 (2H, d, J = 8 Hz), 7.35 (2H, d, J = 8 Hz), 7.33 (1H, s), 7.30 (1H, d, J = 8 Hz), 7.21 (1H, d, J = 2 Hz), 7.03 (1H, dd, J = 8, 2 Hz), 1.66 (4H, s), 1.26 (6H, s), 1.20 (3H, s), 1.19 (3H, s).

DMO36 (1.10 g) was obtained by hydrolysing the aforesaid high polarity ester (1.40 g) in the same way.

¹H-NMR (400 MHz, CDCl₃+DMSO-d₆) 8.57 (1H, s), 8.07 (2H, d, J = 8 Hz), 7.32 (1H, d, J = 8 Hz), 7.17 (2H, d, J = 8 Hz), 7.11 (1H, d, J = 2 Hz), 7.09 (1H, s), 6.89 (1H, dd, J = 8, 2 Hz), 1.68 (4H, s), 1.27 (6H, s), 1.21 (3H, s), 1.17 (3H, s).

Example 13

Production of 4-[(5,6,7,8 tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-(imidazol-1-yl)methyl] benzoic acid (DMO32)

Compound III-2 and imidazole were used as the starting material, and, according to the process in accordance with Example 11, DMO32 was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.95 (2H, d, J = 8 Hz), 7.66 (1H, s), 7.33 (1H, d, J = 8 Hz), 7.22 (2H, d, J = 8 Hz), 7.12 (2H, br s), 6.97 (1H, s), 6.90 (1H, dd, J = 8, 2 Hz), 6.87 (1H, s), 1.63 (4H, s), 1.22 (6H, s), 1.16 (3H, s), 1.14 (3H, s).

Example 14

Production of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl anthracen-2-yl)-tetrazoyl] methyl] benzoic acid (DMO33) (Scheme 4)

To anhydrous THF solution (30 ml) of p-formyl benzoic acid methyl ester (6.2 g), Grignard solution (THF, 30 ml) of 2-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl anthracene (IV-1, 10 g) prepared separately was added dropwise under ice-cooling over a period of about one hour. The reaction mixture was stirred at room temperature for two hours, and thereafter, it was discharged into iced water and extraction was carried out with ethyl acetate. The organic phase was concentrated under reduced pressure, and the residue

was purified using silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1) and Compound IV-2 (6.5 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.98 (2H, d, J = 8 Hz), 7.75 (2H, d, J = 8 Hz), 7.73 (1H, d, J = 2 Hz), 7.68 (1H, d, J = 8 Hz), 7.48 (2H, d, J = 8 Hz), 7.26 (1H, dd, J = 8, 2 Hz), 5.98 (1H, d, J = 3 Hz), 3.88 (3H, s), 2.42 (1H, d, J = 3 Hz), 1.76 (4H, s), 1.38 (6H, s), 1.37 (6H, s).

1H-tetrazole (0.131 g) and one drop of concentrated sulfuric acid were added to Compound IV-2 (0.502 g) dissolved in acetic acid (2 ml) and the mixture was stirred at room temperature for 17 hours. The reaction solution was discharged into iced water and the precipitated solid body was filtered and was dried, and thereafter, it was purified using silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) and Compound IV-3 (TLC low polarity isomer, 0.212 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.60 (1H, m), 8.04 (2H, d, J = 8 Hz), 7.77 (1H, s), 7.74 (1H, d, J = 8 Hz), 7.71 (1H, s), 7.56 (1H, d, J = 2 Hz), 7.50 (1H, s), 7.33 (2H, d, J = 8 Hz), 7.26 (1H, dd, J = 8, 2 Hz), 3.91 (3H, s), 1.75 (4H, s), 1.37 (6H, s), 1.36 (6H, br s).

5N sodium hydroxide aqueous solution (0.5 ml) was added to Compound IV-3 (0.197 g) dissolved in ethanol (5 ml) and the mixture was stirred at 50°C for three hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue, and hydrochloric acid aqueous solution was added while cooling to 0°C, and the mixture was made acidic. Extraction of the mixture was carried out with ethyl acetate, and the obtained residue was recrystallised with light petroleum, and DMO33 (0.190 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.60 (1H, s), 8.06 (2H, d, J = 8 Hz), 7.77 (1H, s), 7.74 (1H, d, J = 8 Hz), 7.71 (1H, s), 7.56 (1H, d, J = 2 Hz), 7.51 (1H, s), 7.31 (2H, d, J = 8 Hz), 7.26 (1H, dd, J = 8, 2 Hz), 1.75 (4H, s), 1.37 (6H, s), 1.36 (6H, br s).

Example 15

Production of 4-[4-hydroxyphenyl-(3-isopropyl-4-methoxyphenyl) methyl] benzoic acid (DMO40) (Scheme 5)

Under argon atmosphere, dimethylsulphate (27 ml) was added slowly dropwise to anhydrous 2-butanone solution (300 ml) of o-isopropylphenol (V-1, 25.67 g) and potassium carbonate (77.32 g), and thereafter, it was stirred at about 70°C for ten hours. The reaction solution was filtered after cooling, and the filtrate was concentrated under reduced pressure, and 1N sodium hydroxide aqueous solution (150 ml) was added to the obtained residue. The mixture was stirred at room temperature for 12 hours, and thereafter, extraction was carried out with dichloromethane. The organic phase was

concentrated under reduced pressure and the obtained residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) and Compound V-2 (25.94 g) was obtained as an oily substance.

¹H-NMR (400 MHz, CDCl₃) 7.21 (1H, dd, J = 7.5, 1.7 Hz), 7.15 (1H, ddd, J = 8, 7.5, 1.7 Hz), 6.92 (1H, ddd, J = 7.5, 7.5, 1 Hz), 6.84 (1H, dd, J = 8, 1 Hz), 3.82 (3H, s), 3.32 (1H, m, J = 7 Hz), 1.21 (6H, d, J = 7 Hz).

To anhydrous dichloromethane solution (300 ml) of Compound V-2 (17.23 g) and monomethyl terephthalic acid chloride (25.44 g), aluminum chloride (23.61 g) was added slowly under water cooling, and this mixture was stirred at room temperature for 18 hours. The reaction mixture was discharged into hydrochloric acid aqueous solution including ice and extraction was carried out with dichloromethane. The solvent was eliminated by distillation under reduced pressure, and the residue was recrystallised from n-hexane, and Compound V-3 (23.31 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 8.14 (2H, d, J = 8.6 Hz), 7.80-7.78 (3H, m), 7.63 (1H, dd, J = 8.5, 2.5 Hz), 6.88 (1H, d, J = 8.5 Hz), 3.96 (3H, s), 3.91 (3H, s), 3.34 (1H, m, J = 7 Hz), 1.21 (6H, d, J = 7 Hz).

To anhydrous THF solution (25 ml) of Compound V-3 (2.0 g), 1-bromo-4-methoxymethoxy benzene (1.52 g) dissolved in Grignard (THF, 6ml) prepared separately was added slowly dropwise under ice cooling, and thereafter, the mixture was stirred at room temperature for one hour. The reaction liquor was discharged into iced water, and extraction was carried out with ethyl acetate, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1-3 : 1) and Compound V-4 (0.88 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.96 (2H, d, J = 8.8 Hz), 7.40 (2H, d, J = 8.8 Hz), 7.16 (2H, d, J = 8.8 Hz), 7.13 (1H, d, J = 2.4 Hz), 6.95 (2H, d, J = 8.8 Hz), 6.91 (1H, dd, J = 8.8, 2.4 Hz), 6.73 (1H, d, J = 8.8 Hz), 5.15 (2H, s), 3.89 (3H, s), 3.80 (3H, s), 3.46 (3H, s), 3.26 (1H, m, J = 7 Hz), 2.85 (1H, s), 1.11 (6H, d, J = 7 Hz).

Concentrated hydrochloric acid (three drops) was added to Compound V-4 (0.80 g) dissolved in THF (10 ml) and the mixture was stirred at about 50°C for five hours. The reaction solution was cooled and water was added and extraction was carried out with ethyl acetate. The organic phase was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) and Compound V-5 (0.49 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.95 (2H, d, J = 8.7 Hz), 7.39 (2H, d, J = 8.7 Hz), 7.79 (1H, d, J = 2.5 Hz), 7.08 (2H, d, J = 8.8 Hz), 6.90 (1H, dd, J = 8.5, 2.5 Hz), 6.76 (2H, d, J = 8.8 Hz), 6.73 (1H, d, J = 8.5 Hz), 5.68 (1H, s), 3.90 (3H, s), 3.80 (3H, s), 3.25 (1H, m, J = 7 Hz), 2.85 (1H, s), 1.10 (6H, d, J = 7 Hz).

Pd-C (0.05 g) was added to Compound V-5 (0.14 g) dissolved in ethanol (13 ml) and the mixture was stirred for two hours under hydrogen atmosphere. The reaction solution was filtered by passing through activated charcoal, and the solvent was eliminated by distillation under reduced pressure. The residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) and Compound V-6 (0.11 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.94 (2H, d, J = 8.5 Hz), 7.18 (2H, d, J = 8.5 Hz), 6.94 (3H, m), 6.72 (1H, dd, J = 8.3, 2.4 Hz), 6.75 (2H, d, J = 8.5 Hz), 6.74 (1H, d, J = 8.5 Hz), 5.46 (1H, s), 5.25 (1H, s), 3.89 (3H, s), 3.76 (3H, s), 3.25 (1H, m, J = 7 Hz), 1.12 (6H, d, J = 7 Hz).

1N sodium hydroxide aqueous solution (1 ml) was added to Compound V-6 (0.06 g) dissolved in ethanol (7 ml) and the mixture was stirred at about 50°C for six hours, and thereafter the reaction liquor was concentrated under reduced pressure. Water was added to the residue, and hydrochloric acid aqueous solution was added while cooling to 0°C, and the mixture was formed into acidic, thereafter, extraction was carried out with ethyl acetate.

The obtained residue was recrystallised with diethyl ether-light petroleum, and DMO40 (0.04 g) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.94 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 6.95 (1H, d, J = 2.5 Hz), 6.90 (2H, d, J = 8.5 Hz), 6.81 (1H, dd, J = 8.5, 2.5 Hz), 6.76 (2H, d, J = 8.5 Hz), 6.73 (1H, d, J = 8.5 Hz), 5.43 (1H, s), 3.79 (3H, s), 3.24 (1H, m, J = 7 Hz), 1.12 (6H, d, J = 7 Hz).

Example 16

Production of 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl)-(1,2,4-triazol-1-yl) methyl] benzoic acid (DM130)

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalene-2-yl) carbonyl] benzoic acid methyl ester (5.0 g) is dissolved in the mixed solution of tetrahydrofuran (250 ml) and methanol (100 ml), and, at room temperature, sodium borohydride is added till the raw

material disappears. After the raw material had disappeared, the reaction mixture was discharged into iced water, and extraction was carried out with ether. By concentrating the organic phase under reduced pressure, the reductant was obtained quantitatively. This was dissolved in 250 ml tetrahydrofuran, and the mixture was stirred for 24 hours under water cooling while hydrochloric acid gas was blew. The reaction mixture was concentrated under reduced pressure, and by repeating recrystallising the residue from n-hexane, the crystals of 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) chloromethyl] benzoic acid methyl ester (4.0 g) were obtained.

¹H-NMR (400 MHz, CDCl₃) 8.02 (2H, d, J = 8 Hz), 7.47 (2H, d, J = 8 Hz), 7.30 (1H, s), 7.07 (1H, s), 6.30 (1H, s), 3.91 (3H, s), 2.27 (3H, s), 1.65 (4H, s), 1.27 (3H, s), 1.26 (3H, s), 1.25 (3H, s), 1.15 (3H, s).

Using 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) chloromethyl] benzoic acid methyl ester and 1,2,4-triazole as starting materials, DM130 was obtained according to the process in accordance with Example 11.

¹H-NMR (400 MHz, CDCl₃) 8.11 (2H, d, J = 8 Hz), 8.08 (1H, s), 7.84 (1H, s), 7.14 (1H, s), 7.12 (2H, d, J = 8 Hz), 6.93 (1H, s), 6.67 (1H, s), 2.17 (3H, s), 1.62 (4H, br s), 1.27 (3H, s), 1.27 (3H, s), 1.08 (3H, s), 1.01 (3H, s).

Example 17

Production of 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO10) (Scheme 6).

6-amino-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (VI-1, 1.214 g, 5.97 mmol), 4-iodobenzoic acid ethyl (1.622 g, 5.87 mmol) and tert-BuONa (600 mg) were dissolved in anhydrous toluene 60 ml, and, under argon substitution, tris (dibenzylideneacetone) dipalladium (0) 97.0 mg, (R) -BINAP 158 mg were introduced and heated at 80°C. One hour was allowed to pass, and it was cooled to room temperature, and introduced into water 200 ml, and extraction was carried out with ether.

The organic layer was dewatered with magnesium sulfate, and after concentration, it was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 19 : 1) and 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) was obtained 1.0 g (48 %).

¹H-NMR (400 MHz, CDCl₃) 7.91 (2H, d, J = 8.8 Hz), 7.27 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.6 Hz), 6.96 (1H, dd, J = 2.6, 8.8 Hz), 6.94 (2H, d, J = 9.2 Hz), 4.33 (2H, q, J = 7.0 Hz), 1.69 (4H, s), 1.37 (3H, t, J = 7.3 Hz), 1.28 (6H, s), 1.27 (6H, s).

Compound VI-2 (118 mg) was dissolved in ethanol (4 ml) and 20% KOH aqueous solution (0.5 ml) was added and refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid 30 ml and extraction was carried out with methylene chloride. The organic layer was dewatered with anhydrous sodium sulfate, and thereafter, it was concentrated, and DAO10 was obtained as white crystals 109 mg (quantitative).

Pale colored prisms (acetic acid-n-hexane); mp 277°C

¹H-NMR (400 MHz, CDCl₃+DMSO-d₆) 7.89 (2H, dt, J = 1.0, 8.8 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.2 Hz), 6.98 (1H, dd, J = 2.6, 8.4 Hz), 6.97 (2H, dt, J = 1.8, 8.8 Hz), 6.78 (1H, br s), 1.69 (4H, s), 1.28 (6H, s), 1.27 (6H, s).

Anal. Calcd. for C₂₁H₂₅NO₂, C: 77.98%, H: 7.79%, N: 4.33%;

Found C: 78.02%, H: 8.01%, N = 4.29 %.

Example 18

Production of 4-[N-methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO11) (Scheme 6).

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 242 mg was dissolved in DMF 2ml, and NaH (145 mg) suspended in DMF (2 ml) was added. Thereafter, methyl iodide (1.5 ml) was added and the mixture was stirred at room temperature. Raw material disappearance was confirmed with TLC, and thereafter the reaction liquor was discharged into water (50 ml) and extraction with methylene chloride was carried out. The organic layer was dewatered with magnesium sulfate, and after concentration, it was refined by flash silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) and 4-[N-methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester 269 mg (quantitative) was obtained.

Colorless needles (n-hexane); mp 131°C.

¹H-NMR (400 MHz, CDCl₃) 7.86 (2H, dd, J = 2.2, 9.16 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.13 (1H, d, J = 2.6 Hz), 6.95 (1H, dd, J = 2.2, 8.4 Hz), 6.74 (2H, dd, J = 2.2, 9.2 Hz), 4.32 (2H, q, J = 7.0 Hz), 3.34 (3H, s), 1.70 (4H, s), 1.36 (3H, t, J = 7.3 Hz), 1.30 (6H, s), 1.25 (6H, s).

Anal. Calcd. for C₂₄H₃₁NO₂, C: 78.86%, H: 8.55%, N: 3.83%;

Found C: 78.88%, H: 8.68%, N = 3.78 %.

The aforesaid ester body 367 mg was dissolved in ethanol 5 ml, and 20% KOH aqueous solution 1 ml was added, and it was refluxed. After the raw materials had disappeared, the

reaction liquor was discharged into 1N hydrochloric acid 50 ml and extraction was carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and thereafter, it was concentrated, and DAO11 was obtained as white crystals 334.5 mg (quantitative).

Colorless powders (n-hexane); mp 252°C.

¹H-NMR (400MHz, CDCl₃) 7.92 (2H, dd, J = 1.8, 9.2 Hz), 7.35 (1H, d, J = 8.4 Hz), 7.17 (1H, d, J = 2.2 Hz), 6.98 (1H, dd, J = 2.6, 8.4 Hz), 6.76 (2H, dd, J = 2.2, 9.2 Hz), 3.38 (3H, s), 1.73 (4H, s), 1.33 (6H, s), 1.28 (6H, s).

Anal. Calcd. for C₂₂H₂₇NO₂, C: 78.30%, H: 8.07%, N: 4.15%;

Found C: 78.16%, H: 8.14%, N = 4.16 %.

Example 19

Production of 4-[N-ethyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO12).

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 249 mg was dissolved in DMF (5 ml) and NaH (134mg) suspended in DMF (5 ml) was added. Thereafter, ethyl iodide (3 ml) was added and the mixture was stirred at room temperature. Raw material disappearance was confirmed with TLC, and thereafter the reaction liquor was discharged into water (50 ml) and extraction with methylene chloride was carried out. The organic layer was dewatered with magnesium sulfate, and after concentration, it was refined by flash silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) and 4-[N-ethyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester 269 mg (quantitative) was obtained.

Colorless needles (n-hexane); mp 88.5°C.

¹H-NMR (400 MHz, CDCl₃) 7.83 (2H, dd, J = 1.8, 9.2 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 2.2, 8.1 Hz), 6.65 (2H, dd, J = 2.2, 9.2 Hz), 4.31 (2H, q, J = 7.3 Hz), 3.76 (2H, q, J = 7.0 Hz), 1.70 (4H, t), 1.35 (3H, t, J = 7.3 Hz), 1.30 (6H, s), 1.24 (6H, s), 1.24 (3H, t, J = 7.3 Hz).

Anal. Calcd. for C₂₅H₃₃NO₂, C: 79.11%, H: 8.76%, N: 3.69%;

Found C: 78.84%, H: 8.86%, N = 3.40 %.

The aforesaid ester body (270 mg) was dissolved in ethanol (8 ml) and 20% KOH aqueous solution 2 ml was added and refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid (40 ml) and extraction was

carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and thereafter, it was concentrated, and DAO12 was obtained as white crystals 251 mg (quantitative).

Colorless powders (n-hexane-methylene chloride); mp 256°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, d, J = 9.2 Hz), 7.33 (1H, d, J = 8.4 Hz), 7.11 (1H, s), 6.93 (1H, d, J = 8.4 Hz), 6.65 (2H, d, J = 9.2 Hz), 3.77 (2H, q, J = 7.3 Hz), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 1.25 (3H, t, J = 7.0 Hz).

Anal. Calcd. for C₂₃H₂₉NO₂, C: 78.59%, H: 8.32%, N: 3.99%;

Found C: 78.81%, H: 8.23%, N = 4.09 %.

Example 20

Production of 4-[N-n-propyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO13).

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 252 mg was dissolved in DMF (5 ml) and NaH (135 mg) suspended in DMF (5 ml) was added. Thereafter, n-propyl (3 ml) iodide was added and the mixture was stirred at room temperature. Raw material disappearance was confirmed with TLC, and thereafter the reaction liquor was discharged into water (30 ml) and extraction with methylene chloride was carried out. The organic layer was dewatered with magnesium sulfate, and after concentration, it was refined by flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and white crystal 282 mg (99.6 %) was obtained.

Colorless powder (n-hexane); mp 114°C.

¹H-NMR (400 MHz, CDCl₃) 7.83 (2H, dd, J = 1.8, 8.8 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 2.6 Hz, 8.4 Hz), 6.64 (2H, dd, J = 2.2, 9.2 Hz), 4.31 (2H, q, J = 7.0 Hz), 3.63 (2H, t, J = 7.7 Hz), 1.71 (2H, hex, J = 7.3 Hz), 1.70 (4H, s), 1.35 (3H, t, J = 7.3 Hz), 1.31 (6H, s), 1.25 (6H, s), 0.94 (3H, t, J = 7.3 Hz).

Anal. Calcd. for C₂₆H₃₅NO₂, C: 79.34%, H: 8.96%, N = 3.56%;

Found C: 79.21%, H: 8.75%, N = 3.48 %.

The aforesaid ester body (282 m g) was dissolved in ethanol (8 ml) and 20% KOH aqueous solution (2 ml) was added and refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid (50 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and thereafter, it was concentrated, and DAO13 was obtained as white crystals 262 mg (quantitative).

Colorless powder (n-hexane); mp 235.5°C.

¹H-NMR(400 MHz, CDCl₃) 7.87 (2H, d, J = 9.2 Hz), 7.33 (1H, d, J = 8.1 Hz), 7.11 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 2.6 Hz, 8.4 Hz), 6.63 (2H, d, J = 9.2 Hz), 3.63 (2H, t, J = 7.7 Hz), 1.67-1.76 (2H, m), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 0.94 (3H, t, J = 7.7 Hz).

Anal. Calcd. for C₂₄H₃NO₂, C: 78.86%, H: 8.55%, N: 3.83%;

Found C: 78.64%, H: 8.46%, N = 3.84 %.

Example 21

Production of 4-[N-n-butyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO14).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and n-butyl iodide, DAO14 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 216°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, d, J = 8.8 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.10 (1H, s), 6.93 (1H, d, J = 6-6 Hz), 6.68 (2H, d, J = 9.2 Hz), 3.67 (2H, t, J = 7.7 Hz), 1.70 (4H, s), 1.64-1.74 (2H, m), 1.37 (2H, hex, J = 7.7 Hz), 1.31 (6H, s), 1.25 (6H, s), 0.94 (3H, t, J = 7.3 Hz).

Anal. Calcd. for C₂₅H₃₃NO₂, C: 79.11%, H: 8.76%, N: 3.69%;

Found C: 79.23%, H: 8.68%, N = 3.71 %.

Example 22

Production of 4-[N-n-pentyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO15).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and n-pentyl iodide, DAO15 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 219-221°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, dd, J = 1.8, 8.8 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.11 (1H, d, J = 2.6 Hz), 6.93 (1H, dd, J = 2.6, 8.4 Hz), 6.63 (2H, dd, J = 1.83, 9.2 Hz), 3.66 (2H, t, J = 7.7 Hz), 1.70 (4H, s), 1.66-1.70 (2H, m), 1.31 (6H, s), 1.25 (6H, s), 1.22-1.37 (4H, m), 0.89 (3H, t, J = 7.0 Hz).

Anal. Calcd. for C₂₆H₃₅NO₂, C: 79.34%, H: 8.97%, N: 3.56%;

Found C: 79.05%, H: 8.95%, N = 3.44 %.

Example 23

Production of 4-[N-n-hexyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO16).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and n-hexyl iodide, DAO16 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 199-200.5°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, dd, J = 2.2, 9.2 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.10 (1H, d, J = 2.6 Hz), 6.93 (1H, dd, J = 2.6, 8.4 Hz), 6.63 (2H, dd, J = 1.8, 8.8 Hz), 3.67 (2H, t, J = 7.7 Hz), 1.70 (4H, s), 1.65-1.70 (2H, m), 1.31 (6H, s), 1.25 (6H, s), 1.29-1.46 (6H, m), 0.88 (3H, t, J = 7.0 Hz).

Anal. Calcd. for C₂₇H₃₇NO₂, C: 79.56%, H: 9.15%, N: 3.44%;

Found C: 79.53%, H: 8.94%, N = 3.14 %.

Example 24

Production of 4-[N-n-heptyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO17).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and n-heptyl iodide, DAO17 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 168°C.

¹H-NMR (400 MHz, CDCl₃) 7.86 (2H, d, J = 9.2 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 1.8 Hz), 6.93 (1H, dd, J = 2.2, 8.4 Hz), 6.63 (2H, d, J = 8.8 Hz), 3.66 (2H, t, J = 7.7 Hz), 1.70 (4H, s), 1.70 (2H, br m), 1.31 (6H, s), 1.25-1.31 (8H, br m), 1.25 (6H, s), 0.87 (3H, t, J = 6.6 Hz).

Anal. Calcd. for C₂₈H₃₉NO₂, C: 79.76%, H: 9.32%, N: 3.32%;

Found C: 79.80%, H: 9.52%, N = 3.06 %.

Example 25

Production of 4-[N-n-octyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO18).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and n-octyl iodide, DAO18 was synthesised according to process of Example 20.

Colorless cotton (n-hexane-methylene chloride); mp 160°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, dd, J = 2.2, 9.2 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.2 Hz), 6.92 (1H, dd, J = 2.2, 8.4 Hz), 6.63 (2H, d, J = 9.2 Hz), 3.66 (2H, t, J

= 8.1 Hz), 1.70 (4H, s), 1.70 (2H, m), 1.31 (6H, s), 1.26 (10H, m), 1.25 (6H, s), 0.87 (3H, t, J = 6.6 Hz).

Anal. Calcd. for C₂₉H₄NO₂, C: 79.95%, H: 9.49%, N: 3.22%;

Found C: 79.92%, H: 9.54%, N = 3.18 %.

Example 26

Production of 4-[N-(propine-3-yl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO20).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and acetylenyl methyl bromide, DAO20 was synthesised according to process of Example 20.

Colorless prisms (n-hexane-methylene chloride); mp 269-270°C (dec).

¹H-NMR(400 MHz, CDCl₃) 7.93 (2H, dd, J = 2.2, 9.2 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.21 (1H, d, J = 2.2 Hz), 7.03 (1H, dd, J = 2.2, 8.4 Hz), 6.80 (2H, dd, J = 2.2, 9.2 Hz), 4.41 (2H, d, J = 2.6 Hz), 2.29 (1H, t, J = 2.2 Hz), 1.71 (4H, s), 1.31 (6H, s), 1.25 (6H, s).

Example 27

Production of 4-[N-(propen-3-yl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO21).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and allyl bromide, DAO21 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 247-248°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, dd, J = 1.8, 9.2 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.16 (1H, d, J = 2.2 Hz), 6.98 (1H, dd, J = 2.2, 8.1 Hz), 6.71 (2H, dd, J = 1.8, 9.2 Hz), 5.94 (1H, ddt, J = 5.2, 10.3, 17.2 Hz), 5.28 (1H, dd, J = 1.5, 17.2 Hz), 5.22 (1H, dd, J = 1.5, 10.3 Hz), 4.35 (1H, dd, J = 1.8, 4.8 Hz), 1.70 (4H, s), 1.30 (6H, s), 1.24 (6H, s).

Anal. Calcd. for C₂₄H₂₉NO₂, C: 79.30%, H: 8.04%, N: 3.85%;

Found C: 79.08%, H: 8.18%, N = 4.15 %.

Example 28

Production of 4-[N-isopropyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO22).

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 113 mg and potassium carbonate (89 mg) were dissolved in isopropyl iodide, and it was refluxed for 48 hours. The reaction liquor was discharged in water (30 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with

magnesium sulfate, and after elimination of the solvent, it was refined using flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and 13 mg (10 %) was obtained.

Colorless prisms (n-hexane); mp 81°C.

¹H-NMR (400 MHz, CDCl₃) 7.80 (2H, dd, J = 2.2, 9.2 Hz), 7.33 (1H, d, J = 8.4 Hz), 6.99 (1H, d, J = 2.2 Hz), 6.82 (1H, dd, J = 2.2, 8.4 Hz), 6.50 (2H, dd, J = 2.6, 9.2 Hz), 4.35 (1H, hep, J = 6.6 Hz), 4.29 (2H, q, J = 7.0 Hz), 1.71 (4H, s), 1.33 (3H, t, J = 7.0 Hz), 1.31 (6H, s), 1.24 (6H, s), 1.14 (6H, d, J = 6.6 Hz).

The aforesaid ester body (45 m g) was dissolved in ethanol (4 ml) and 20% KOH aqueous solution (1 ml) was added and refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid (30 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with anhydrous sodium sulfate, and the solvent was eliminated by distillation, and DAO22 of 40 mg (98 %) was obtained.

Colorless powder (n-hexane-methylene chloride); mp 259°C.

¹H-NMR (400 MHz, CDCl₃) 7.85 (2H, dd, J = 2.2, 9.2 Hz), 7.34 (1H, d, J = 8.4 Hz), 6.99 (1H, d, J = 2.2 Hz), 6.82 (1H, dd, J = 2.2, 8.1 Hz), 6.51 (2H, d, J = 9.2 Hz), 4.37 (1H, hep, J = 6.6 Hz), 1.71 (4H, s), 1.32 (6H, s), 1.24 (6H, s), 1.15 (6H, d, J = 6.6 Hz).

Example 29

Production of 4-[N-cyclopropyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO23).

Cyclopropylamine (1 ml) and 4-iodobenzoic acid ethyl (407 m g) and tert-BuONa (180 mg) were dissolved in anhydrous toluene (10 ml), and, under argon substitution, tris (dibenzylideneacetone) dipalladium (0) (54 m g) and (R)-BINAP (102 mg) were added and heated at 80°C. After four hours, it was cooled to room temperature, and it was discharged into water 30 ml and extraction was carried out with ether.

The organic layer was dewatered with anhydrous sodium sulfate, and after concentration, it was refined using flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and 4-(cyclopropyl amino) benzoic acid ethyl ester was obtained 150 mg (56 %).

Colorless needles (n-hexane); mp 69°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, dd, J = 2.2, 8.8 Hz), 6.74 (2H, dd, J = 2.2, 8.8 Hz), 4.53 (1H, br s), 4.32 (2H, q, J = 7.0 Hz), 2.48 (1H, dt, J = 1.5, 2.6, 6.2 Hz), 1.36 (3H, t, J = 7.0 Hz), 0.79 (2H, ddd, J = 4.4, 6.6, 7.0 Hz), 0.54 (2H, ddd, J = 3.7, 4.8, 6.6 Hz).

Anal. Calcd. for C₂₁H₁₅NO₂, C: 70.22%, H: 7.37%, N: 6.83%;

Found C: 70.20%, H: 7.23%, N: 6.68 %.

4-(cyclopropyl amino) benzoic acid ethyl ester (97 mg), 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (121.5 mg) and tert-BuONa (67 mg) were dissolved in anhydrous toluene (5 ml) and, under argon substitution, tris (dibenzylideneacetone) dipalladium (0) (24 mg) and (R)-BINAP (40.5 mg) were added and heated at 80°C. One hour 30 minutes was allowed to pass, and thereafter, it was cooled to room temperature, and it was discharged in water 30 ml, and extraction was carried out with methylene chloride. The organic layer was washed with saturated aqueous sodium chloride solution, and it was dewatered with anhydrous sodium sulfate, and after concentration, it was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and 4-[N-cyclopropyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester 42 mg (20 %) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.86 (2H, dd, J = 2.2, 9.2 Hz), 7.29 (1H, d, J = 8.1 Hz), 7.02 (1H, d, J = 2.6 Hz), 6.93 (2H, dd, J = 1.8, 8.8 Hz), 6.87 (dd, J = 2.2, 8.1 Hz), 4.31 (2H, q, J = 7.3 Hz), 2.80 (1H, tt, J = 3.7, 6.6 Hz), 1.70 (4H, s), 1.35 (3H, t, J = 7.3 Hz), 1.30 (6H, s), 1.24 (6H, s), 0.89 (2H, ddd, J = 4.8, 6.2, 7.0 Hz), 0.63 (2H, ddd, J = 3.7, 5.1, 7.0 Hz).

The aforesaid ester body (42 mg) was dissolved in ethanol (2 ml) and 20% KOH aqueous solution (0.5 ml) was added and refluxed. After two hours, the reaction liquor was discharged in 1N NaOH aqueous solution (30 ml) and it was washed with ether, and the aqueous layer was made strong acid with concentrated hydrochloric acid, and extraction was carried out with methylene chloride. The organic layer was dewatered with anhydrous sodium sulfate, and thereafter, it was concentrated, and yellowish white crystals 14 mg (35 %) were obtained. The obtained crystals were treated with activated carbon, and thereafter, DAO23 was obtained as white crystal by recrystallization.

Colorless prisms (n-hexane-methylene chloride); mp 260-261°C (dec).

¹H-NMR (400 MHz, CDCl₃) 7.89 (2H, dd, J = 2.2, 9.2 Hz), 7.30 (1H, d, J = 8.43 Hz), 7.02 (1H, d, J = 2.2 Hz), 6.94 (1H, dd, J = 2.2, 9.2 Hz), 6.87 (2H, dd, J = 2.2, 8.4 Hz), 2.82 (1H, tt, J = 4.0, 7.0 Hz), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 0.90 (2H, ddd, J = 5.1, 6.6, 7.0 Hz), 0.64 (2H, ddd, J = 5.1, 5.5, 7.3 Hz).

Example 30

Production of 4-[N-cyclopropylmethyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO24).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and cyclopropylmethyl bromide, DAO24 was synthesised according to process of Example 20.

Colorless prisms (nr hexane-methylene chloride); mp 245°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, dd, J = 1.8, 9.2 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 2.6 Hz), 6.95 (1H, dd, J = 2.2, 8.1 Hz), 6.68 (2H, dd, J = 1.8, 9.2 Hz), 3.56 (2H, d, J = 6.6 Hz), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 1.15-1.22 (1H, m), 0.50 (2H, ddd, J = 4.4, 5.9, 8.1 Hz), 0.14 (2H, q, J = 4.8 Hz).

Anal. Calcd. for C₂₅H₃₃NO₂, C: 79.53%, H: 8.28%, N: 3.71%;

Found C: 79.33%, H: 8.36%, N = 3.82 %.

Example 31

Production of 4-[N-isobutyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO25).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and isobutyl iodide, DAO25 was synthesised according to process of Example 20.

Colorless prisms (n-hexane-methylene chloride); mp 232°C.

¹H-NMR(400 MHz, CDCl₃) 7.85 (2H, dd, J = 1.8, 9.2 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.12 (1H, d, J = 2.6 Hz), 6.93 (1H, dd, J = 2.2, 8.4 Hz), 6.67 (2H, d, J = 9.2 Hz), 3.52 (2H, d, J = 7.3 Hz), 2.08 (1H, 7th, J = 7.0 Hz), 1.70 (4H, s), 1.30 (6H, s), 1.24 (6H, s), 0.96 (6H, d, J = 6.6 Hz).

Anal. Calcd. for C₂₅H₃₃NO₂, C: 79.11%, H: 8.76%, N: 3.69%;

Found C: 79.10%, H: 8.81%, N = 3.65 %.

Example 32

Production of 4-[N-iso pentenyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO28).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and prenyl bromide, DAO28 was synthesised according to process of Example 20.

Colorless prisms (n-hexane-methylene chloride); mp 215°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, dd, J = 2.2, 9.2 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.11 (1H, d, J = 2.2 Hz), 6.94 (1H, dd, J = 2.2, 8.4 Hz), 6.67 (2H, dd, J = 2.2, 9.2 Hz), 5.33 (1H, t, J = 5.86 Hz), 4.29 (2H, d, J = 5.49 Hz), 1.72 (3H, s), 1.70 (4H, s), 1.61 (3H, s), 1.30 (6H, s), 1.24 (6H, s).

Example 33

Production of 4-[N-cyclobutyl methyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl) amino] benzoic acid (DAO30).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and cyclobutyl methyl bromide, DAO30 was synthesised according to process of Example 20.

Colorless needles (n-hexane-methylene chloride); mp 232°C.

¹H-NMR (400 MHz, CDCl₃) 7.85 (2H, dd, J = 2.2, 9.2 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 2.2 Hz), 6.89 (1H, dd, J = 2.2, 8.4 Hz), 6.60 (2H, dd, J = 1.8, 8.8 Hz), 3.70 (2H, d, J = 7.0 Hz), 2.74 (1H, 5th, J = 7.7 Hz), 2.01 (2H, m), 1.82 (2H, m), 1.70 (4H, s), 1.66 (2H, m), 1.30 (6H, s), 1.24 (6H, s).

Anal. Calcd. for C₂₆H₃₃NO₂, C: 79.75%, H: 8.50%, N: 3.58%;

Found C: 79.82%, H: 8.53%, N = 3.61 %.

Example 34

Production of 4-[N-cyclohexylmethyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO36).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and cyclohexyl bromide methyl, DAO36 was synthesised according to process of Example 20.

Colorless cubes (n-hexane-methylene chloride); mp 230-231°C.

¹H-NMR (400 MHz, CDCl₃) 7.86 (2H, d, J = 9.2 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.10 (1H, d, J = 2.2 Hz), 6.92 (1H, dd, J = 2.2, 8.4 Hz), 6.65 (2H, dd, J = 9.2 Hz), 3.59 (2H, d, J = 7.0 Hz), 1.75 (6H, m), 1.70 (4H, s), 1.31 (6H, s), 1.24 (6H, s), 1.16 (3H, m), 0.95 (2H, m).

Anal. Calcd. for C₂₈H₃₇NO₂, C: 80.15%, H: 8.89%, N: 3.34%;

Found C: 79.86%, H: 8.89%, N = 3.33 %.

Example 35

Production of 4-[N-benzyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO40).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl) amino] benzoic acid ethyl ester (VI-2) and benzyl bromide, DAO40 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 272-273°C.

¹H-NMR (400 MHz, CDCl₃) 7.84 (2H, dd, J = 2.2, 9.2 Hz), 7.32 (4H, d, J = 4.8 Hz), 7.80 (1H, d, J = 7.3 Hz), 7.28-7.25 (1H, m), 7.21 (1H, d, J = 2.2 Hz), 7.04 (1H, dd, J = 2.2, 8.4 Hz), 6.73 (2H, dd, J = 1.8, 9.2 Hz), 5.00 (2H, s), 1.69 (4H, s), 1.29 (6H, s), 1.22 (6H, s).

Anal. Calcd. for C₂₈H₃, NO₂, C: 81.32%, H: 7.56%, N: 3.39%;

Found C: 81.05%, H: 7.49%, N = 3.57 %.

Example 36

Production of 4-[N-(4-methylbenzyl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO41).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and (4-methylbenzyl) bromide, DAO41 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 246-248°C.

¹H-NMR (400 MHz, CDCl₃) 7.83 (2H, dd, J = 2.2, 9.2 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.21 (1H, d, J = 2.2 Hz), 7.20 (2H, d, J = 6.6 Hz), 7.12 (2H, d, J = 8, 1Hz), 7.03 (1H, dd, J = 2.2, 8.4 Hz), 6.73 (2H, dd, J = 2.9, 9.2 Hz), 4.96 (2H, s), 2.32 (3H, s), 1.68 (4H, s), 1.29 (6H, s), 1.22 (6H, s).

Anal. Calcd. for C₂₉H₃₃NO₂, C: 81.46%, H: 7.78%, N: 3.28%;

Found C: 81.28%, H: 7.82%, N = 3.44 %.

Example 37

Production of 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)-N-(4-trifluoromethyl benzyl) amino] benzoic acid (DAO42).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and (4-trifluoromethyl benzyl) bromide, DAO42 was synthesised according to process of Example 20.

Colorless powder (n-hexane); mp 209-210°C.

¹H-NMR (400MHz, CDCl₃) 7.86 (2H, dd, J = 2.2, 9.2 Hz), 7.58 (2H, d, J = 8.1 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.19 (1H, d, J = 2.2 Hz), 7.2 (1H, dd, J = 2.2, 8.4 Hz), 6.70 (2H, d, J = 8.8 Hz), 5.04 (2H, s), 1.69 (4H, s), 1.29 (6H, s), 1.22 (6H, s).

Anal. Calcd. for C₂₉H₃₀NO₂F₃, C: 72.33 %, H: 6.28%, N: 2.91%;

Found C: 72.15%, H: 6.41%, N = 2.94 %.

Example 38

Production of 4-[N-(4-ethoxy-2,3,5,6-tetrafluoro benzyl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO45).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and (pentafluorobenzyl) bromide, DAO45 was synthesised according to process of Example 20.

Colorless powder (n-hexane - methylene chloride); mp 227-229°C.

¹H-NMR (400 MHz, CDCl₃) 7/90 (2H, dd, J=1.8, 8.8 Hz), 7.26 (1H, d, J = 8.4 Hz), 6.98 (1H, d, J = 2.2 Hz), 6.87 (1H, dd, J = 2.2, 8.4 Hz), 6.75 (2H, dd, J = 1.8, 8.8 Hz), 4.92 (2H, s), 4.22 (q, J = 7.0 Hz), 1.66 (4H, s), 1.36 (3H, t, J = 7.0 Hz), 1.25 (6H, s), 1.16 (6H, s).

Anal. Calcd. for C₃₀H₃₃F₄NO₃, C: 68.04%, H: 5.90%, N: 2.65%;

Found C: 67.78%, H: 5.89%, N = 2.61 %.

Example 39

Production of 4-[N-(2-biphenyl methyl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO46).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and biphenyl methyl bromide, DAO46 was synthesised according to process of Example 20.

Colorless prisms (n-hexane-methylene chloride); mp 237-239°C.

¹H-NMR (400 MHz, CDCl₃) 7.80 (2H, d, J = 8.8 Hz), 7.79-7.48 (1H, m), 7.35-7.44 (4H, m), 7.23-7.31 (6H, m), 7.15 (1H, d, J = 2.6 Hz), 6.98 (1H, dd, J = 2.2, 8.8 Hz), 6.64 (2H, d, J = 9.2 Hz), 4.87 (2H, s), 1.68 (4H, s), 1.28 (6H, s), 1.19 (6H, s).

Anal. Calcd. for C₃₄H₃₅NO₂, C: 83.40%, H: 7.21%, N: 2.86%;

Found C: 83.11%, H: 7.50%, N = 2.75 %.

Example 40

Production of 4-[N-(2-naphthylmethyl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO48).

Using 4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) and 2-naphthylmethyl bromide, DAO48 was synthesised according to process of Example 20.

Colorless powder (n-hexane-methylene chloride); mp 233°C.

¹H-NMR (400 MHz, CDCl₃) 7.84 (2H, dd, J = 2.2, 9.2 Hz), 7.78 (4H, m), 7.44 (3H, m), 7.31 (1H, d, J = 8.4 Hz), 7.27 (1H, d, J = 2.6 Hz), 7.09 (1H, dd, J = 2.2, 8.4 Hz), 6.79 (2H, dd, J = 2.2, 9.2 Hz), 5.15 (2H, s), 1.68 (4H, s), 1.28 (6H, s), 1.22 (6H, s).

Anal. Calcd. for C₃₂H₃₃NO₂, C: 82.90%, H: 7.18%, N: 3.02%;

Found C: 82.66%, H: 7.48%, N = 2.73 %.

Example 41

Production of 4-[N-acetyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid (DAO51).

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 605 mg was dissolved in anhydrous toluene (15 ml), and acetyl chloride (1 ml) was added and refluxed under argon overnight. The solvent was distilled off under reduced pressure, and the residue was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) and white crude crystals were obtained 677 mg (quantitative).

Colorless cubes (n-hexane); mp 102°C.

¹H-NMR (400 MHz, CDCl₃) 8.00 (2H, d, J = 8.4 Hz), 7.33 (2H, dd, J = 1.8, 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.15 (1H, d, J = 2.6 Hz), 6.95 (1H, dd, J = 2.2, 8.4 Hz), 4.36 (2H, q, J = 7.0 Hz), 2.05 (3H, s), 1.69 (4H, s), 1.37 (3H, t, J = 7.0 Hz), 1.28 (6H, s), 1.24 (6H, s).

Anal. Calcd. for C₂₅H₃₁NO₃, C: 76.30%, H: 7.94%, N: 3.56%;

Found C: 76.26%, H: 7.93%, N = 3.51 %.

The aforesaid ester body (404 mg) was dissolved in ethanol (10 ml) and 5% NaOH aqueous solution (0.9 ml) was added and the mixture was stirred at room temperature overnight. The solvent was distilled off under reduced pressure, and water (0.5 ml) and concentrated hydrochloric acid (5 ml) were added to the residue and the precipitated crystals were recovered by filtration and dried, and DAO51 was obtained as white crystal 342 mg (91 %).

Colorless powder (n-hexane); mp 222°C.

¹H-NMR (400 MHz, CDCl₃) 8.04 (2H, d, J = 8.4 Hz), 7.36 (2H, dd, J = 2.2, 8.8 Hz), 7.33 (1H, d, J = 8.1 Hz), 7.16 (1H, d, J = 2.2 Hz), 6.96 (1H, dd, J = 2.6, 8.4 Hz), 2.06 (3H, s), 1.70 (4H, s), 1.29 (6H, s), 1.25 (6H, s).

Anal. Calcd. for C₂₃H₂₇NO₃, C: 75.59%, H: 7.45%, N: 3.83%;

Found C: 75.29%, H 7.54 %, N = 3.65 %.

Example 42

Production of 4-[N-benzoyl-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl) amino] benzoic acid (DAO55)

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 104 mg was dissolved in anhydrous benzene (5 ml) and benzoyl chloride (1 ml) and pyridine (1 ml) were added, and it was stirred. After the raw materials had disappeared, the reaction liquor was discharged to saturated aqueous sodium bicarbonate and extraction was carried out with methylene chloride. The organic layer was washed

with 1N hydrochloric acid (30 ml), and it was dewatered with anhydrous sodium sulfate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and white crude crystals 130 mg (96.5 %) were obtained.

Colorless powder (n-hexane-methylene chloride); mp 149°C.

¹H-NMR (400 MHz, CDCl₃) 7.97 (2H, d, J = 8.4 Hz), 7.41 (2H, d, J = 8.4 Hz), 7.18-7.30 (6H, m), 6.91 (1H, d, J = 2.2 Hz), 6.84 (1H, dd, J = 2.6, 8.4 Hz), 4.36 (2H, q, J = 7.0 Hz), 1.61 (4H, s), 1.38 (3H, t, J = 6.96 Hz), 1.23 (6H, s), 1.02 (6H, s).

Anal. Calcd. for C₃₀H₃₃NO₃, C: 79.09%, H: 7.30%, N: 3.08%;

Found C: 78.94%, H: 7.29%, N: 3.08 %.

The aforesaid ester body (79 mg) was dissolved in ethanol (4 ml) and 5% NaOH aqueous solution (1 ml) was added, and the mixture was stirred at room temperature for five hours. The reaction liquor was discharged into 1N hydrochloric acid and extraction was carried out with methylene chloride. The organic layer was dewatered with anhydrous sodium sulfate, and the solvent was eliminated by distillation, and DAO55 77 mg (quantitative) was obtained.

Colorless cotton (n-hexane-methylene chloride); mp 228-229.5°C.

¹H-NMR (400 MHz, CDCl₃) 8.03 (2H, dd, J = 1.8, 8.8 Hz), 7.42 (2H, dd, J = 1.5Hz, 8.4 Hz), 7.19-7.30 (6H, m), 6.91 (1H, d, J = 2.6 Hz), 6.85 (1H, dd, J = 2.6Hz, 8.4 Hz), 1.61 (4H, s), 1.23 (6H, s), 1.02 (6H, s).

Anal. Calcd. for C₂₈H₂₉NO₃, C: 78.66%, H: 6.84%, N: 3.28%;

Found C: 78.77%, H: 6.95%, N = 8.19 %.

Example 43

Production of 4-[N-(4-carboxy benzoyl)-N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl) amino] benzoic acid (DAO58)

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl) amino] benzoic acid ethyl ester (VI-2) 153.0 mg was dissolved in anhydrous benzene (5 ml) and monomethyl terephthalic acid ester chloride (210 mg) and two drops of pyridine were added, and it was stirred. After the raw materials had disappeared, the reaction liquor was discharged to saturated aqueous sodium bicarbonate and extraction was carried out with methylene chloride.

The organic layer was washed with 1N hydrochloric acid (30 ml), and it was dewatered with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure, and the residue was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) and white crude crystals 191 mg (quantitative) were obtained.

Colorless powder (n-hexane); mp 135°C.

¹H-NMR (400 MHz, CDCl₃) 7.98 (2H, d, J = 8.4 Hz), 7.88 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.24 (2H, d, J = 8.4 Hz), 7.21 (1H, d, J = 8.4 Hz), 6.92 (1H, s), 6.84 (1H, dd, J = 2.2, 8.4 Hz), 4.36 (2H, q, J = 7.3 Hz), 3.89 (3H, s), 1.61 (4H, s), 1.38 (3H, t, J = 7.0 Hz), 1.23 (6H, s), 1.03 (6H, s).

Anal. Calcd. for C₃₂H₃₅NO₅, C: 74.83%, H: 6.87% N: 2.73%;

Found C: 74.75%, H: 7.00%, N: 2.44 %.

The aforesaid ester body (86.3 mg) was dissolved in ethanol (50 ml), and 5% NaOH aqueous solution (2 ml) was added, and the mixture was stirred at room temperature for four hours. The reaction liquor was discharged to 1N hydrochloric acid and extraction was carried out with methylene chloride and ethyl acetate. The organic layer was dewatered with magnesium sulfate, and the solvent was eliminated by distillation, and DAO58 was obtained as white crystals 78.2 mg (98.8 %).

Colorless powder (n-hexane); mp >300°C.

¹H-NMR (400 MHz, CDCl₃) 7.90 (2H, d, J = 8.4 Hz), 7.78 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.1 Hz), 7.43 (1H, s), 7.35 (2H, d, J = 8.4 Hz), 7.29 (1H, d, J = 8.4 Hz), 6.92 (1H, d, J = 8.4 Hz), 1.56 (4H, s), 1.18 (6H, s), 1.02 (6H, s).

Example 44

Production of 4-[N-ethyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid (DA112) (Scheme 7)

1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene (VII-1, 21.888 g) was dissolved in acetic acid (80 ml) and mixed acid of hydrochloric acid and sulfuric acid was added under ice cooling slowly, and the mixture was stirred at room temperature.

After Three hours, the reaction liquor was discharged in water (200 ml) and the precipitated crystals were recovered by filtration, and they were washed with water, and thereafter, they were dissolved in methylene chloride. This organic layer was successively washed with saturated aqueous sodium bicarbonate and aqueous sodium chloride, and it was dewatered with magnesium sulfate, and the solvent was eliminated by distillation. The obtained crude crystals were recrystallised from methanol, and 7-nitro-1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene (VII-2) 14.59 g (54.5 %) was obtained as white crystals.

¹H-NMR (400 MHz, CDCl₃) 7.96 (1H, s), 7.21 (1H, s), 2.56 (3H, s), 1.72 (4H, s), 1.30 (6H, s), 1.29 (6H, s).

The aforesaid nitro body (VII-2) 14.59g was dissolved in ethyl acetate (200 ml) and ethanol (100 ml), and 10% Pd/C (1.74 g) was added, and catalytic reduction was carried out. The reaction liquor was filtered with cellite, and crude crystals obtained by elimination of the filtrate by distillation was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 25 : 1) and 7-amino-1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene (VII-3) 12.14 g (94.6 %) was obtained as yellowish white crystals.

¹H-NMR (400 MHz, CDCl₃) 6.98 (1H, s), 6.63 (1H, s), 3.61 (2H, br s), 2.14 (3H, s), 1.64 (4H, s), 1.24 (12H, s).

The aforesaid amino body (VII-3) 1.085g, 4-iodo ethyl benzoate (1.676 g) and tert-BuONa (616 mg) were dissolved in anhydrous toluene (20 ml) and under argon substitution, tris (dibenzylidene acetone) dipalladium (0) (101.5 mg) and (R)-BIMP (163.8 mg) were added, and the mixture was refluxed. After Three hours, the reaction liquor was cooled to room temperature, and discharged to water 100 ml, and extraction was carried out with ether. The organic layer was dewatered with anhydrous sodium sulfate, and it was concentrated, and thereafter the residue was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) and 4-[N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid ethyl ester (VII-4) 1.095 g (60 %) was obtained.

Colorless needles (n-hexane); mp 173-175°C.

¹H-NMR (400 MHz, CDCl₃) 7.89 (2H, dd, J = 1.83Hz, 8.8 Hz), 7.21 (1H, s), 7.16 (1H, s), 6.77 (2H, dd, J = 1.8Hz, 8.8 Hz), 4.33 (2H, q, J = 7.0 Hz), 2.19 (3H, s), 1.68 (4H, s), 1.37 (3H, t, J = 7.0 Hz), 1.29 (6H, s), 1.24 (6H, s).

Anal. Calcd. for C₂₄H₃₁NO₂, C: 78.86%, H: 8.55%, N: 3.83%;

Found C: 79.05%, H: 8.80%, N: 3.58 %.

The aforesaid amino body (VII-4, 92 mg) was dissolved in DMF (2 ml) and NaH (61.5 mg) suspended in DMF (2 ml) was added. Thereafter, ethyl iodide (1 ml) was added and the mixture was stirred at room temperature. The disappearance of the raw materials was confirmed with TLC, and thereafter the reaction liquor was discharged into water (30 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and after concentration, it was purified by flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and 4-[N-ethyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid ethyl ester 98 mg (99 %) was obtained.

Colorless powder (n-hexane); mp 94°C.

¹H-NMR(400 MHz, CDCl₃) 7.83 (2H, d, J = 8.8 Hz), 7.20 (1H, s), 7.00 (1H, s), 6.43 (2H, d, J = 9.2 Hz), 4.30 (2H, q, J = 7.3 Hz), 3.66 (2H, d, J = 6.6 Hz), 2.03 (3H, s), 1.69 (4H, s), 1.34 (3H, t, J = 7.0 Hz), 1.31 (6H, s), 1.25 (3H, t, J = 7.3 Hz), 1.23 (6H, s).

Anal. Calcd. for C₂₆H₃₅NO₂, C: 79.34%, H: 8.96%, N: 3.56%;

Found C: 79.12%, H: 8.93%, N: 3.57 %.

The aforesaid ester body (83 mg) was dissolved in ethanol (4 ml) and 20% KOH aqueous solution 1 ml was added, and it was refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid (40 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and the solvent was eliminated by distillation, and DA112 77 mg (quantitative) was obtained.

Colorless powder (n-hexane-methylene chloride); mp 266°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, d, J = 9.2 Hz), 7.20 (1H, s), 7.00 (1H, s), 6.45 (2H, d, J = 8.8 Hz), 3.67 (2H, br), 2.04 (1H, s), 1.69 (4H, s), 1.31 (6H, s), 1.26 (3H, t, J = 7.0 Hz), 1.23 (6H, s).

Anal Calcd. for C₂₄H₃₁NO₂, C: 78.86%, H: 8.55%, N: 3.83%;

Found C: 78.56%.

H: 8.71 %, N: 3.82 %.

Example 45

Production of 4-[N-n-propyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid (DA113)

Using Compound VII-4 and n-propyl iodide, DA113 was synthesised according to the process of Example 44.

Colorless powder (n-hexane); mp 245°C.

¹H-NMR (400 MHz, CDCl₃) 7.86 (2H, d, J = 9.2 Hz), 7.20 (1H, s), 7.00 (1H, s), 6.42 (2H, d, J = 8.8 Hz), 3.52 (2H, br s), 2.02 (3H, s), 1.72 (2H, hep, J = 7.7 Hz), 1.69 (4H, s), 1.31 (6H, s), 1.23 (6H, s), 0.95 (3H, t, J = 7.7 Hz).

Anal. Calcd. for C₂₅H₃₃NO₂, C: 79.11%, H: 8.76%, N: 3.69%;

Found C: 79.17%, H: 8.89%, N: 3.64 %.

Example 46

Production of 4-[N-isopropyl methyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid (DA122)

Compound VII-4 (299 mg) and potassium carbonate (499 mg) were dissolved in isopropyl iodide and the mixture was heated in sealed tube at 150°C for seven days. The reaction liquor was filtered, and the filtrate was dewatered with anhydrous sodium sulfate, and it was concentrated. The obtained residue was purified by flash column chromatography (n-hexane : ethyl acetate = 20 : 1) and colourless transparent oily substance 7 mg (2%) was obtained.

¹H-NMR(400 MHz, CDCl₃) 7.82 (2H, d, J = 9.2 Hz), 7.18 (1H, s), 6.91 (1H, s), 6.41 (2H, d, J = 8.8 Hz), 4.34 (1H, hept, J = 7.0 Hz), 4.29 (2H, q, J = 7.3 Hz), 2.01 (3H, s), 1.69 (4H, s), 1.33 (3H, t, J = 7.3 Hz), 1.30 (6H, s), 1.22 (6H, s), 1.15 (6H, s).

The aforesaid ester body (12 mg) was dissolved in ethanol (3 ml) and 20% KOH aqueous solution 0.5 ml were added, and the mixture was refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid (20 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and the solvent was eliminated by distillation, and DA122 was obtained.

Colorless cubes (n-hexane-methylene chloride); mp 257°C.

¹H-NMR (400 MHz, CDCl₃) 7.85 (2H, d, J = 9.2 Hz), 7.19 (1H, s), 6.91 (1H, s), 6.43 (2H, d, J = 9.2 Hz), 4.36 (1H, pent, J = 7.0 Hz), 2.01 (3H, s), 1.69 (4H, s), 1.31 (6H, s), 1.23 (6H, s), 1.16 (6H, brs).

Example 47

Production of 4-[N-cyclopropylmethyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid (DA124)

Using Compound VII-4 and cyclopropylmethyl bromide, DA124 was synthesised according to the process of Example 44.

Colorless plates (n-hexane-methylene chloride); mp 213°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, d, J = 9.2 Hz), 7.17 (1H, s), 6.50 (2H, d, J = 8.8 Hz), 3.50 (2H, br s), 2.03 (3H, s), 1.69 (4H, s), 1.30 (6H, s), 1.24 (6H, s), 1.22 (1H, m), 0.51 (2H, ddd, J = 4.8, 5.5, 8.1 Hz), 0.13 (2H, q, J = 4.8 Hz).

Example 48

Production of 4-[N-isobutyl-N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl naphthalen-2-yl) amino] benzoic acid (DA125).

Using Compound VII-4 and isobutyl iodide, DA125 was synthesised according to the process of Example 44.

Colorless cotton (n-hexane-methylene chloride); mp 245°C.

¹H-NMR (400 MHz, CDCl₃) 7.85 (2H, d, J = 9.2 Hz), 7.18 (1H, s), 7.07 (1H, s), 6.44 (2H, d, J = 9.2 Hz), 3.40 (2H, br s), 1.67 (1H, hept, J = 7.0 Hz), 1.98 (3H, s), 1.69 (4H, s), 1.31 (6H, s), 1.24 (6H, s), 0.99 (6H, d, J = 6.6 Hz).

Example 49

Production of 4-[N-ethyl-N-(3,5-di-tert-butylphenyl) amino] benzoic acid (DA212) (Scheme 8).

3,5-di-tert-butyl aniline (VIII-1) 1.087 g, 4-iodobenzoic acid ethyl (1817 g) and tert-BuONa (667.5 mg) were dissolved in anhydrous toluene (20 ml), and under argon substitution, tris (dibenzylideneacetone) dipalladium (0) 106 mg and (R)-BINAP (176 mg) were added, and it was refluxed. After two hours, the reaction liquor was cooled to room temperature, and discharged to water (100 ml) and extraction was carried out with ether. The organic layer was dewatered with anhydrous sodium sulfate, and it was concentrated, and thereafter the residue was purified using flash silica gel column chromatography (n-hexane : ethyl acetate = 20 : 1) and 4-[N-(3,5-di-tert-butylphenyl) amino] benzoic acid ethyl ester (VIII-2) 1.28 g (68 %) was obtained.

Colorless needles (n-hexane); mp 123°C.

¹H-NMR (400 MHz, CDCl₃) 7.92 (2H, dd, J = 1.8, 8.8 Hz), 7.14 (1H, t, J = 1.8 Hz), 7.03 (2H, d, J = 1.5 Hz), 6.96 (2H, dd, J = 1.8, 8.8 Hz), 6.01 (1H, br s), 4.33 (2H, q, J = 7.3 Hz), 1.37 (3H, t, J = 7.0 Hz), 1.32 (18H, s).

Anal. Calcd. for C₂₃H₃₁NO₂, C: 78.14%, H: 8.84%, N: 3.96%;

Found C: 78.33%, H: 8.94%, N: 3.69 %.

The aforesaid amino body (VIII-2) 101 mg was dissolved in DMF (2 ml) and NaH 90 mg suspended in DMF (2 ml) was added. Thereafter, ethyl iodide (1 ml) was added and the mixture was stirred at room temperature.

Disappearance of the raw materials was confirmed with TLC, and thereafter the reaction liquor was discharged into water (30 ml) and extraction with methylene chloride was carried out.

The organic layer was dewatered with magnesium sulfate, and after concentration, it was refined by flash silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) and 4-[N-ethyl-N-(3,5-di-tert-butylphenyl) amino] benzoic acid ethyl ester (99 %) was obtained.

Colorless powder (n-hexane); mp 90°C.

¹H-NMR (400 MHz, CDCl₃) 7.83 (2H, dd, J = 2.2, 9.2 Hz), 7.31 (1H, t, J = 1.8 Hz), 7.02 (2H, d, J = 1.5 Hz), 6.64 (2H, dd, J = 2.2, 9.2 Hz), 4.31 (2H, q, J = 7.0 Hz), 3.79 (2H, q, J = 7.0 Hz), 1.35 (3H, t, J = 7.0 Hz), 1.32 (18H, s), 1.26 (3H, t, J = 7.0 Hz).

Anal. Calcd. for C₂₅H₃₅NO₂, C: 78.69%, H: 9.25%, N: 3.67%;

Found C: 78.77%, H: 9.09%, N = 3.69 %.

The aforesaid ester body (89 mg) was dissolved in ethanol (4 ml) and 20% KOH aqueous solution (1 ml) was added and the mixture was refluxed. After the raw materials had disappeared, the reaction liquor was discharged in 1N hydrochloric acid (30 ml) and extraction was carried out with methylene chloride. The organic layer was dewatered with magnesium sulfate, and the solvent was eliminated by distillation, and DA212 80 mg (97 %) was obtained.

Colorless prisms (n-hexane-methylene chloride); mp 225°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, dd, J = 2.2, 9.2 Hz), 7.33 (1H, t, J = 1.8 Hz), 7.02 (2H, d, J = 1.8 Hz), 6.68 (2H, dd, J = 1.8, 8.8 Hz), 3.80 (2H, q, J = 7.0 Hz), 1.32 (18H, s), 1.27 (3H, t, J = 7.0 Hz)

Anal. Calcd. for C₂₃H₃₁NO₂, C: 78.14%, H: 8.84%, N: 3.96%;

Found C: 78.20%

H: 8.91 %, N: 3.92 %.

Example 50

Production of 4-[N-n-propyl-N-(3,5-di-tert-butylphenyl) amino] benzoic acid ethyl ester (DA213).

Using Compound VIII-2 and n-propyl iodide, DA213 was synthesised according to the process of Example 49.

Colorless prisms (n-hexane-methylene chloride); mp 247-248°C.

¹H-NMR (400 MHz, CDCl₃) 7.87 (2H, dd, J = 2.2, 9.2 Hz), 7.03 (2H, d, J = 1.8 Hz), 6.61 (2H, dd, J = 1.8, 9.2 Hz), 3.66 (2H, t, J = 7.7 Hz), 1.74 (2H, hex, J = 7.7 Hz), 1.82 (18H, s), 0.95 (3H, t, J = 7.7 Hz).

Anal. Calcd. for C₂₄H₃₃NO₂, C: 78.43%, H: 9.05%, N: 3.81%;

Found C: 78.55%, H: 8.94%, N: 3.59 %.

Example 51

Production of 4-[N-phenyl-N-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl naphthyl)] amino] benzoic acid (TA001)

4-[N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl) amino] benzoic acid ethyl ester (VI-2) 107 mg, phenyl iodide 0.1ml and tert-BuONa 33.5 mg were dissolved in

anhydrous toluene 5 ml, and under argon substitution, tris (dibenzylideneacetone) dipalladium (0) 21 mg and BINAP (Registered Trade Name) 43 mg were added and the mixture was heated at 80°C. After one hour 40 minutes, tert-BuONa 33 mg was added. Furthermore after one hour 50 minutes, it was cooled to room temperature, and the mixture was discharged to water 30 ml, and extraction was carried out with methylene chloride. The organic layer was dewatered with sodium sulfate and concentrated and hereafter, refined using flash silica gel column chromatography (n-hexane : ethyl acetate = 40 : 1) and 4-[N-phenyl-N-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl naphthyl)] amino] benzoic acid ethyl ester 28 mg (y. 22%) was obtained.

¹H-NMR (400 MHz, CDCl₃) 7.84 (2H, dd, J = 1.8, 8.8 Hz), 7.29 (2H, t, J = 7.3 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.08-7.16 (4H, m), 6.97 (2H, dd, J = 1.8, 8.8 Hz), 6.82 (1H, dd, J = 2.6, 8.4 Hz), 4.33 (2H, q, J = 7.3 Hz), 1.67 (4H, s), 1.36 (3H, t, J = 7.3 Hz), 1.28 (6H, s), 1.17 (6H, s).

The aforesaid ester body 23 mg was dissolved in ethanol 3 ml, and 20% KOH aqueous solution 0.5 ml were added and refluxed for one hour. The reaction liquor was discharged to 1N hydrochloric acid and extraction was carried out with methylene chloride. The organic layer was dewatered with anhydrous sodium sulfate, and the solvent was eliminated by distillation, and yellowish white crystals 21 mg (quantitative) were obtained.

The obtained crystals were treated with activated charcoal, and thereafter, white crystals were obtained by recrystallization.

TA001: colorless prism (n-hexane-methylene chloride); mp 239°C.

¹H-NMR (400 MHz, CDCl₃) 7.88 (2H, dd, J = 1.8, 8.8 Hz), 7.31 (2H, t, J = 8.4 Hz), 7.22 (1H, d, J = 8.4 Hz), 7.17 (2H, dd, J = 1.5, 8.8 Hz), 7.12 (1H, t, J = 7.3 Hz), 7.10 (1H, d, J = 2.6 Hz), 6.97 (2H, dd, J = 2.2, 9.2 Hz), 6.84 (2H, dd, J = 2.6, 8.4 Hz), 1.68 (4H, s), 1.28 (6H, s), 1.18 (6H, s).

Example 52

Production of 4-[N,N-bis [2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl naphthyl)] amino] benzoic acid (TAO12).

Under nitrogen atmosphere, the mixture of p-ethyl aminobenzoate (7.42 g), 2-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (10 g), potassium carbonate (10.4 g), copper oxidation (0.5 g) and nitrobenzene (5 ml) was stirred at about 220°C for five hours. The reaction mixture was cooled and thereafter, ether was added and the mixture was filtered. Ether phase was washed with water, and the solvent was eliminated by distillation under reduced pressure, and the residue was purified using silica gel column

chromatography (n-hexane : ethyl acetate = 1 : 5) and Compound VI-2 (3.5 g) and 4-[N,N-bis [2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl naphthyl)] amino] benzoic acid ethyl ester (3.1 g) were obtained.

Bis body: $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.82 (2H, d, $J = 9$ Hz), 7.19 (2H, d, $J = 8$ Hz), 7.08 (2H, d, $J = 2$ Hz), 6.94 (2H, d, $J = 9$ Hz), 6.84 (2H, dd, $J = 8, 2$ Hz), 4.32 (2H, q), 1.67 (8H, s), 1.35 (3H, t), 1.27 (12H, s), 1.17 (12H, s).

Aqueous solution (3 ml) of sodium hydroxide (0.67 g) was added to 4-[N,N-bis [2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl naphthyl)] amino] benzoic acid ethyl ester (3 g) dissolved in ethanol (20 ml) and the mixture was stirred at 50°C for three hours. The reaction mixture was concentrated under reduced pressure. Water was added to the residue, and during cooling to 0°C , hydrochloric acid aqueous solution was added, and the mixture was neutralized. extraction of the mixture was carried out with ethyl acetate, and the obtained residue was purified by column chromatography (ethyl acetate) and TAO12 (1.5 g) was obtained.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.87 (2H, d, $J = 9$ Hz), 7.21 (2H, d, $J = 8$ Hz), 7.10 (2H, d, $J = 2$ Hz), 6.93 (2H, d, $J = 9$ Hz), 6.86 (2H, dd, $J = 8, 2$ Hz), 1.67 (8H, s), 1.27 (12H, s), 1.18 (12H, s).

Test Example

Calibration of cytodifferentiation induction in H-60 cell

On each compound, cytodifferentiation induction action and the effect with respect to cytodifferentiation induction action of the retinoid which coexisted were examined independently. Am80 [4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) carbamoyl] benzoic acid or retinoic acid was used as retinoid were caused to be copresent and a comparison made. In accordance with the process described in Kokai 61-76440, differentiation to granulocyte system was assessed by form change and reducibility measurement of nitroblue tetrazolium (NBT) using promyelocytic leukemia cell strain HL-60. In Table 1, the concentration-dependent effect with respect to the concentration-dependent differentiation inducibility of each compound alone, and with respect to the differentiation inducibility of $1 \times 10^{-9}\text{M}$ retinoic acid (RA) or Am80 are shown. The concentration-dependent effect of each compound with respect to differentiation inducibility of $1 \times 10^{-10}\text{M}$ Am80 is shown in Table 2. In Table 3, the concentration-dependent effect with respect to the concentration-dependent differentiation inducibility of each compound alone and the differentiation inducibility of $1 \times 10^{-10}\text{M}$ Am80 are shown. Moreover, the rates (%) of differentiated cells which are shown in the following

each table have been calculated from NBT reducibility, and concentration is s by logarithm value, and “-“ denotes one which is not measured.

Table 1

Compound	Rate (%) of the differentiated cell of the compound alone				Rate (%) of the differentiated cell which are co-existed with 1 X 10 ⁻⁹ M Am80				Rate (%) of the differentiated cell which are co-existed with 1 X 10 ⁻⁹ M RA		
	-8	-7	-6	None	-8	-7	-6	None	-8	-7	
DM010	1	0	-	66	76	89	-	14	26	66	
DM012	0	1	1	66	73	85	94	14	57	69	
DM030	1	1	4	66	68	94	90	14	58	73	
DM032	1	1	17	66	58	90	88	14	-	-	

Table 2

		Rate (%) of the differentiated cell which is copresent with 1 X 10 ⁻¹⁰ M Am80				
Compounds	Concentration					
	None	-10	-9	-8	-7	-6
DM021	4.5	-	6	12	43	83
DM030	15.5	38	41	43	81	90
DM031	4.5	8	14	41	81	86
DM032	15.5	36	39	46	81	87

Table 3

Compounds	Rate (%) of the differentiated cell of the compound alone					Rate (%) of the differentiated cell which is co-present with 1 X 10 ⁻¹⁰ M Am80				
	Concentration					Concentration				
	-9	-8	-7	-6	None	-10	-9	-8	-7	-6
DA010	1.7	2.7	3.2	61	12	-	34	38	46	89
DA011	2.4	3.6	5	81	12	-	43	49	85	91
DA012	-	1.3	6.7	15.2	4.5	10	21	80	89	-
DA013	-	1	4	3.3	4.5	18	28	87	90	-
DA014	-	2.1	4.5	3.2	14	-	36	69	92	57
DA015	-	2.3	2.6	2.3	14	-	28	50	65	47
DA021	-	3.4	2.5	8.2	4.5	8.1	9.6	42	90	-
DA022	-	2.8	3.8	5.5	5.5	42	55	89	-	-
DA023	-	2	3.9	6.8	5.5	39	67	95	-	-
DA024	-	4.3	8.3	6.6	5.5	24	48	87	-	-
DA030	-	0.9	2.7	1.6	4	12	55	87	86	47
DA051	-	2.5	3.3	3	14	-	31	32	46	74
DA112	-	3.5	5	4	5.5	40	71	90	-	-
DA113	-	2.1	2.2	4.3	5.5	37	80	94	-	-
DA212	-	1.5	1.8	2.5	4.5	4.8	8.5	8	45	66
DA213	-	1.3	0.6	0.9	4.5	8	17	74	88	66

Test Example 2

Hypoglycemic action with respect to diabetes mellitus model mouse

Blood was collected from the tail vein of KK mouse of 4-5 month old which had onset of diabetes mellitus, and blood glucose level thereof was measured. Next, mice were classified to groups so that the average of blood glucose level of mice of each group (one group was 4 mice) become same, and mice of each group were given powder feed for mouse (F1, Funabashi plantation) prepared to include 0.01-0.03 % test substance for three days. As contrast, the powder feed which did not include drug was administered to contrast mouse. Blood was collected from the mouse tail vein after 3 days, and the glucose concentration in plasma obtained by centrifugation was measured with glucose analyser and Glucolader-F (A&T Co., Ltd.). Hypoglycemic rate of test substance was determined by the following formula. Hypoglycemic rate (%) = ([blood glucose level of contrast mouse] - [blood glucose level of mouse administrated drug]) / [blood glucose level of contrast mouse].

Table 4

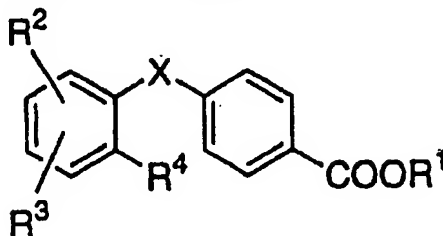
Compounds	Concentration (%) in feed	Blood glucose level (mean value)	Hypoglycaemic rate (%)
Contrast		455 ± 10	
DA011	0.03	383 ± 38	15.9
DA051	0.03	462 ± 38	-1.4
DM010	0.03	431 ± 14	5.4
DM011	0.03	396 ± 44	13.1
DM030	0.03	416 ± 17	8.7
DM031	0.03	326 ± 30	28.3
Contrast		452 ± 38	
DA012	0.01	282 ± 47	37.6
DA012	0.03	352 ± 61	22.2
DA013	0.01	426 ± 53	5.9
DA013	0.03	430 ± 25	4.9
Contrast		374 ± 51	
DA012	0.03	255 ± 26	31.7

Possible Applications in Industry

The compounds of this invention have the action to regulate physiologically active expression of retinoid such as retinoic acid or the like, and therefore it is useful as effective ingredient of drug such as retinoid action adjuster or the like.

Patent Claims

1. A compound or salts thereof which is represented by the following general formula (1)



(wherein, R¹ denotes a hydrogen atom or C1-6 alkyl group;

R², R³ and R⁴ independently denote hydrogen atom, C1-6 alkoxy group or 1-6C alkyl group, or when R² and R³ are adjacent, they are together and 5- or 6-membered ring may be formed together with the carbon atom on the phenyl group where R² and R³ link (the aforesaid ring may contain 1, 2 or more 1-4C alkyl groups or condensed benzene ring optionally having 1, 2 or more substituents on the ring thereof); and

X denotes divalent group represented by -C(R⁵)(R⁶)- or -NR⁷-

(wherein, R⁵ denotes a hydrogen atom or hydroxy group; R⁶ denotes optionally substituted phenyl group or optionally substituted 5- or 6-membered saturated or unsaturated nitrogen-containing heterocyclic group; and R⁷ denotes a hydrogen atom, C1-12 alkyl group optionally having 1, 2 or more unsaturated bonds, C3-12 cycloalkyl group, C4-12 cycloalkyl substituted alkyl group, optionally substituted aralkyl group, C1-12 alkanoyl group, optionally substituted aroyl group or optionally substituted phenyl group)).

2. A drug which includes, as an active ingredient, substances selected from the group comprising compounds in accordance with Claim 1 and salts thereof, their hydrates and their solventate which are physiologically acceptable.

3. A drug in accordance with Claim 2 which is retinoid action adjuster.

4. A drug in accordance with Claim 2 or 3 which is used as action promoter or action depressant of the physiologically active substance which combines with a intranuclear receptor belonging to intranuclear receptor superfamily, and display physiological action.

5. A drug in accordance with Claim 4, wherein the said physiologically active substance is retinoid.

6. Composition for drug including the substance selected from the group comprising compounds in accordance with Claim 1 and the salts thereof, their hydrates and their solventate which are pharmacologically acceptable, and retinoid.
7. Use of the substance selected from the group comprising compounds in accordance with Claim 1 for the production of the drug in accordance with any one of Claims 2-5 and the salts thereof, their hydrates and their solventate which are pharmacologically acceptable.
8. A process to regulate the action of retinoid in vivo of mammalian organism and is the process including the step to administer effective dose of the substance selected from the group comprising compounds in accordance with Claim 1 and the salts thereof, their hydrates and their solventate which are pharmacologically acceptable to mammalian organism including human being.
9. A process in accordance with Claim 8 that is prevention and/or therapeutic process of vitamin A deficiency, dermatosis, allergic disease, immunologic disease, bone disease, Alzheimer's disease, Huntington's chorea or malignant tumor.
10. A process in accordance with Claim 8 that is prevention and/or therapeutic process of diabetes mellitus, arteriosclerosis, hyperlipidemia or hypercholesterolemia.
- 11.

Rising Sun Communications Ltd. Terms and Conditions (Abbreviated)

Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.

Rising Sun Communications Ltd. retains the copyright to all of its' translation products unless expressly agreed in writing to the contrary. The original buyer is permitted to reproduce copies of a translation for their own corporate use at the site of purchase, however publication in written or electronic format for resale or other dissemination to a wider audience is strictly forbidden unless by prior written agreement.

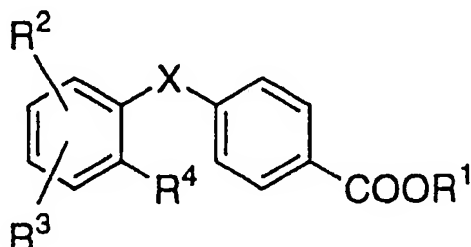
The Full Terms and Conditions of Business of Rising Sun Communications may be found at the web site address <http://www.risingsun.co.uk/Terms_of_business.html>



<p>(51) 国際特許分類6 C07C 63/49, 65/24, 229/54, 229/62, 233/65, 233/81, C07D 249/08, 257/04, 233/56, 295/08, 295/14, A61K 31/415, 31/41, 31/39, C07D 31/395, A61K 31/445, 31/40, 31/535</p>	<p>A1</p>	<p>(11) 国際公開番号 WO98/45242</p> <p>(43) 国際公開日 1998年10月15日(15.10.98)</p>
<p>(21) 国際出願番号 PCT/JP98/01211</p> <p>(22) 国際出願日 1998年3月20日(20.03.98)</p> <p>(30) 優先権データ 特願平9/89450 1997年4月8日(08.04.97) JP 特願平10/41490 1998年2月24日(24.02.98) JP</p> <p>(71) 出願人；および (72) 発明者 影近弘之(KAGECHIKA, Hiroyuki)[JP/JP] 〒178-0062 東京都練馬区大泉町2-39-6 Tokyo, (JP)</p> <p>(72) 発明者；および (75) 発明者／出願人（米国についてのみ） 首藤紘一(SHUDO, Koichi)[JP/JP] 〒168-0073 東京都杉並区下高井戸5-9-18 Tokyo, (JP) 杉岡龍夫(SUGIOKA, Tatsuo)[JP/JP] 早乙女智美(SOTOME, Tomomi)[JP/JP] 中山由紀(NAKAYAMA, Yuki)[JP/JP] 〒350-1165 埼玉県川越市南台1丁目3番地2 ヘキスト・マリオン・ルセル株式会社 創薬研究所内 Saitama, (JP)</p>	<p>土井一之(DOI, Kazuyuki)[JP/JP] 〒350-1165 埼玉県川越市南台1丁目3番地2 ヘキスト・マリオン・ルセル株式会社 情報技術部内 Saitama, (JP)</p> <p>(74) 代理人 弁理士 今村正純, 外(IMAMURA, Masazumi et al.) 〒103-0028 東京都中央区八重洲1丁目8番12号 藤和八重洲一丁目ビル7階 Tokyo, (JP)</p> <p>(81) 指定国 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーロパ特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>添付公開書類 国際調査報告書</p>	
<p>(54)Title: RETINOID ACTIVITY REGULATORS</p> <p>(54)発明の名称 レチノイド作用調節剤</p> <p>(57) Abstract Compounds represented by general formula (I), wherein R¹ represents hydrogen or C₁₋₆ alkyl; R², R³ and R⁴ represent hydrogen, C₁₋₆ alkyl, etc.; and X represents a divalent group -C(R⁵)(R⁶)- or -NR⁷- (wherein R⁵ represents hydrogen or hydroxy; R⁶ represents phenyl or a 5- or 6-membered, saturated or unsaturated nitrogen-containing heterocycle; and R⁷ represents hydrogen, C₁₋₁₂ alkyl optionally having one or more unsaturated bonds, etc.). Because of the effect of regulating the expression of the physiological activities of retinoids such as retinoic acid, these compounds are useful as retinoid activity regulators.</p> <div style="text-align: center;"> <p>(I)</p> </div>		

(57)要約

下記式(I):



(R^1 は水素原子又は C_{1-6} アルキル基を示し; R^2 、 R^3 、及び R^4 は水素原子、 C_{1-6} アルキル基などを示し; X は $-C(R^5)(R^6)-$ 又は $-NR^7-$ で表される二価の基を示す(R^5 は水素原子又は水酸基を示し; R^6 はフェニル基又は5ないし6員の飽和若しくは不飽和の含窒素ヘテロ環基を示し; R^7 は水素原子、1個又は2個以上の不飽和結合を有することもある C_{1-12} アルキル基などを示す))で表される化合物が提供される。上記化合物はレチノイン酸などのレチノイドの生理活性発現を調節する作用を有しており、レチノイド作用調節剤として有用である。

PCTに基づいて公開される国際出願のパンフレット第一頁に掲載されたPCT加盟国を同定するために使用されるコード(参考情報)

AL	アルバニア	FI	フィンランド	LR	リベリア	SK	スロヴァキア
AM	アルメニア	FR	フランス	LS	レソト	SL	シエラ・レオネ
AT	オーストリア	GA	ガボン	LT	リトアニア	SN	セネガル
AU	オーストラリア	GB	英国	LU	ルクセンブルグ	SZ	スワジランド
AZ	アゼルバイジャン	GD	グレナダ	LV	ラトヴィア	TD	チャード
BA	ボスニア・ヘルツェゴビナ	GE	グルジア	MC	モナコ	TG	トーゴ
BB	バルバドス	GH	ガーナ	MD	モルドヴァ	TJ	タジキスタン
BE	ベルギー	GM	ガンビア	MG	マダガスカル	TM	トルクメニスタン
BF	ブルキナ・ファソ	GN	ギニア	MK	マケドニア旧ユーゴスラヴィア	TR	トルコ
BG	ブルガリア	GW	ギニア・ビサウ		共和国	TT	トリニダード・トバゴ
BJ	ベナン	GR	ギリシャ	ML	マリ	UA	ウクライナ
BR	ブラジル	HR	クロアチア	MN	モンゴル	UG	ウガンダ
BY	ベラルーシ	HU	ハンガリー	MR	モーリタニア	US	米国
CA	カナダ	ID	インドネシア	MW	マラウイ	UZ	ウズベキスタン
CF	中央アフリカ	IE	アイルランド	MX	メキシコ	VN	ヴェトナム
CG	コンゴ	IL	イスラエル	NE	ニジェール	YU	ユーゴスラビア
CH	スイス	IS	アイスランド	NL	オランダ	ZW	ジンバブエ
CI	コートジボアール	IT	イタリア	NO	ノールウェー		
CM	カメルーン	JP	日本	NZ	ニュージーランド		
CN	中国	KE	ケニア	PL	ポーランド		
CU	キューバ	KG	キルギスタン	PT	ポルトガル		
CY	キプロス	KP	北朝鮮	RO	ルーマニア		
CZ	チェッコ	KR	韓国	RU	ロシア		
DE	ドイツ	KZ	カザフスタン	SD	スーダン		
DK	デンマーク	LC	セントルシア	SE	スウェーデン		
EE	エストニア	LI	リヒテンシュタイン	SG	シンガポール		
ES	スペイン	LK	スリ・ランカ	SI	スロヴェニア		

明 細 書

レチノイド作用調節剤

技術分野

本発明は、新規化合物に関するものであり、レチノイン酸やレチノイン酸様の生理活性を有する化合物（レチノイド）に代表される核内レセプターリガンドの生理作用を調節する新規化合物に関するものである。本発明の化合物はレチノイド作用調節剤などの医薬の有効成分として有用である。

背景技術

レチノイン酸（ビタミンA酸）はビタミンAの活性代謝産物であり、発生途上にある未熟な細胞を特有な機能を有する成熟細胞へと分化させる作用や、細胞の増殖促進作用や生命維持作用など極めて重要な生理作用を有している。これまでに合成された種々のビタミンA誘導体、例えば、特開昭61-22047号公報や特開昭61-76440号公報記載の安息香酸誘導体、及びジャーナル・オブ・メディシナル・ケミストリー（Journal of Medicinal Chemistry, 1988, Vol. 31, No. 11, p. 2182）に記載の化合物なども、同様な生理作用を有することが明らかにされている。レチノイン酸及びレチノイン酸様の生物活性を有する上記化合物は「レチノイド」と総称されている。

例えば、オール・トランス(all-trans)・レチノイン酸は、細胞核内に存在する核内レセプター・スーパーファミリー（Evans, R. M., Science, 240, p. 889, 1988）に属するレチノイン酸レセプター（RAR）にリガンドとして結合して、動物細胞の増殖・分化あるいは細胞死などを制御することが明らかにされている（Petkovich, M., et al., Nature, 330, pp. 444-450, 1987）。レチノイン酸様の生物活性を有する上記化合物（例えば、4-[(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80など）も、レチノイン酸と同様にRARに結合して生理活性を発揮することが示唆されている（Hashimoto, Y., Cell

struct. Funct., 16, pp.113-123, 1991; Hashimoto, Y., et al., Biochem. Biophys. Res. Commun., 166, pp.1300-1307, 1990を参照)。これらの化合物は、臨床的には、ビタミンA欠乏症、上皮組織の角化症、リウマチ、遅延型アレルギー、骨疾患、及び白血病やある種の癌の治療や予防に有用であることが見出されている。

このようなレチノイドに対して拮抗的に作用し、上記レチノイドの代表的な作用を減弱する化合物が知られている(Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994)。一方、それ自体はレチノイド作用を有しないか、あるいはそのレチノイド作用が微弱であるにもかかわらず、レチノイン酸などのレチノイドの作用を増強する物質についてはほとんど報告がない。例えば、特開平8-59511号公報には、RXR レセプターに対する特異的リガンドである化合物が、RAR- α レセプターに対する特異的なリガンド化合物であるAm80の作用を増強する作用を有することが示唆されている。この刊行物には、4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチル-2- ナフチル) カルボニル] 安息香酸- エチレンアセタールが上記Am80の分化誘導作用を増強することが示唆されている。

また、本発明者は、4-[5H-2, 3-(2, 5- ジメチル-2, 5- ヘキサノ)-5-メチルジベンゾ[b, e][1, 4]ジアゼピン-11-イル] 安息香酸(HX600)などのベンゾジアゼピン化合物がレチノイドの作用を増強することを見いだした(Umemiya et al., Chem. Pharm. Bull., 43, pp.1827-1829, 1995)。この化合物の作用は、RXR-RAR ヘテロダイマーを形成するRXR レセプターを活性化するものと考えられている。

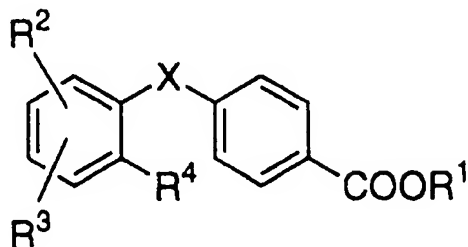
発明の開示

本発明の課題は、レチノイン酸などのレチノイドの作用を調節する作用を有する化合物を提供することにある。より具体的にいうと、それ自体はレチノイド作用を有しないか、あるいはそのレチノイド作用が微弱であるにもかかわらず、レチノイン酸などのレチノイドの作用を増強することができ、あるいはレチノイドの作用を抑制することができる化合物を提供することが本発明の課題である。

本発明者は上記の課題を解決すべく鋭意努力した結果、下記的一般式で示され

る化合物がレチノイン酸などのレチノイドの作用を調節する作用を有していることを見だし、本発明を完成するに至った。

すなわち本発明によれば、下記の一般式(I)：



〔式中、 R^1 は水素原子又は C_{1-6} アルキル基を示し； R^2 、 R^3 、及び R^4 はそれぞれ独立に水素原子、 C_{1-6} アルキル基、若しくは C_{1-6} アルコキシ基を示すか、又は R^2 及び R^3 が隣接する場合にはそれらは一緒になって R^2 及び R^3 が結合するフェニル基上の炭素原子とともに5ないし6員環を形成してもよく（上記の環はその環上に1個または2個以上の C_{1-4} アルキル基を有するか、1個または2個以上の置換基を有することもある1個の縮合ベンゼン環を有していてもよい）； X は $-C(R^5)(R^6)-$ 又は $-NR^7-$ で表される二価の基を示す（式中、 R^5 は水素原子又は水酸基を示し； R^6 は置換基を有することもあるフェニル基、又は置換基を有することもある5ないし6員の飽和若しくは不飽和の含窒素ヘテロ環基を示し； R^7 は水素原子、1個又は2個以上の不飽和結合を有することもある C_{1-12} アルキル基、 C_{3-12} シクロアルキル基、 C_{4-12} シクロアルキル置換アルキル基、置換基を有することもあるアラルキル基、 C_{1-12} アルカノイル基、置換基を有することもあるアロイル基、又は置換基を有することもあるフェニル基を示す）〕で表される化合物またはその塩が提供される。

また、別の観点からは、本発明により、上記化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質を有効成分として含む医薬が提供される。本発明の医薬は、レチノイド作用調節剤、又は核内レセプターリガンド作用調節剤として用いることができる。この発明の好ましい態様によれば、核内レセプター・スーパーファミリーに属する核内レセプターに結合して生理作用を発揮する生理活性物質の作用調節剤として用いる上記の医薬；作用調節が作用増強又は作用抑制である上記の医薬；並びに該

生理活性物質がレチノイドである上記の医薬が提供される。

さらに別の観点からは、本発明により、上記医薬の製造のための、好ましくは医薬組成物の形態の医薬の製造のための上記化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質の使用、並びに、ヒトを含む哺乳類動物の生体内においてレチノイドの作用を調節する方法であって、上記化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質の有効量をヒトを含む哺乳類動物に投与する工程を含む方法が提供される。この方法は、例えば、ビタミンA欠乏症；上皮組織の角化症、乾癬などの皮膚疾患；アレルギー疾患；リウマチなどの免疫性疾患；骨粗鬆症、骨折などの骨疾患；アルツハイマー；ハンチントン舞踏病；白血病又は癌などの疾患の予防及び／又は治療方法、並びに、糖尿病、動脈硬化症、高脂血症、高コレステロール血症、骨疾患、リウマチ、又は免疫性疾患などの疾患の予防及び／又は治療方法として利用できる。さらに、本発明の別の態様により、上記化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質とレチノイドとを含む医薬用組成物が提供される。

発明を実施するための最良の形態

上記の式(I) で表される化合物において、 R^1 は水素原子又は C_{1-6} アルキル基（「 C_{1-6} 」は、その基に含まれる炭素数の総数が1から6個であることを意味し、本明細書中で用いられる他も類似の表現も同様である）アルキル基を示す。アルキル基は直鎖若しくは分枝鎖のいずれであってもよく、例えば、メチル基、エチル基、*n*-プロピル基、イソプロピル基、*n*-ブチル基、*sec*-ブチル基、*tert*-ブチル基などを用いることができる。好ましくはメチル基、エチル基などを用いることができる。

R^2 、 R^3 、及び R^4 はそれぞれ独立に水素原子、 C_{1-6} アルキル基、又は C_{1-6} アルコキシ基を示す。アルキル基は直鎖若しくは分枝鎖のいずれでもよく、例えば、メチル基、エチル基、*n*-プロピル基、イソプロピル基、*n*-ブチル基、*sec*-ブチル基、

tert-ブチル基などを用いることができる。これらのうち、立体的に嵩高いアルキル基、例えば、イソプロピル基、tert-ブチル基などを用いることが好ましい。 C_{1-6} アルコキシ基は直鎖若しくは分枝鎖のいずれでもよく、例えば、メトキシ基、エトキシ基、n-プロポキシ基、イソプロポキシ基、n-ブトキシ基、sec-ブトキシ基、tert-ブトキシ基などを用いることができる。 R^2 及び R^3 の置換位置は特に限定されず、それぞれ独立に任意の位置に置換することができるが、 R^2 及び R^3 が互いに隣接した位置に置換していることが好ましい。例えば、 R^2 及び R^3 がXに対してそれぞれパラ位及びメタ位に存在していることが特に好ましい。

R^2 及び R^3 が隣接した位置に置換する場合には、それらは一緒になって R^2 及び R^3 が結合するフェニル基上の炭素原子とともに5ないし6員環、好ましくは6員環を形成してもよい。このようにして形成される5ないし6員環は、その環上に1個または2個以上の C_{1-4} アルキル基を有していてもよく、例えば、2～4個のメチル基、好ましくは4個のメチル基を有していてもよい。例えば、 R^2 及び R^3 が置換するフェニル基のベンゼン環と R^2 及び R^3 とにより、5,6,7,8-テトラヒドロナフタレン環や5,5,8,8-テトラメチル-5,6,7,8-テトラヒドロナフタレン環などが形成されることが好ましい。

また、 R^2 及び R^3 が結合して形成される5ないし6員環、好ましくは6員環には、1個の縮合ベンゼン環が存在していてもよい。このような場合、 R^2 及び R^3 が結合して形成される5ないし6員環上には1個または2個以上の C_{1-4} アルキル基が存在していてもよく、例えば、2～4個のメチル基、好ましくは4個のメチル基がそれぞれの環上に存在していてもよい。また、縮合ベンゼン環は無置換であってもよいが、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、ハロゲン原子などの置換基を1個または2個以上有していてもよい。例えば、 R^2 及び R^3 が置換するフェニル基のベンゼン環、 R^2 及び R^3 、並びに縮合すべきベンゼン環により、5,6,7,8-テトラヒドロアントラセニル環、5,5,8,8-テトラメチル-5,6,7,8-テトラヒドロアントラセニル環などが形成されていてもよい。 R^4 は水素原子又は C_{1-4} アルキル基であることが好ましい。

Xは $-C(R^5)(R^6)-$ 又は $-N(R^7)-$ で表される二価の基を示す。 R^5 は水素原子又は水酸基を示すが、水素原子であることが好ましい。 R^6 は置換基を有することもあるフ

フェニル基、又は置換基を有することもある5ないし6員の飽和若しくは不飽和の含窒素ヘテロ環基を示す。 R^6 が置換基を有するフェニル基を示す場合、該フェニル基は1個又は2個以上の置換基を有していてもよい。置換基としては、例えば、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、水酸基、ハロゲン原子、ハロゲン化 C_{1-6} アルキル基、カルボキシ基、 C_{1-6} アルコキシカルボニル基、 C_{1-6} アルキルカルボニル基、置換若しくは無置換のアミノ基などを用いることができるが、これらのうち、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、又は水酸基が好ましい。該フェニル基上の置換基の個数及び置換位置は特に限定されないが、p-位に1個の置換基が存在することが好ましい。

R^6 が示す5ないし6員の飽和若しくは不飽和の含窒素ヘテロ環基は、環を構成する原子として少なくとも1個の窒素原子を含んでいればよく、例えば、1-ピロリジニル基、1-ピペリジニル基、モルホリノ基、1-ピペラジニル基などの飽和含窒素ヘテロ環基；3-ピロリン-1-イル基などの不飽和含窒素ヘテロ環基；1-ピロリル基、1-イミダゾリル基、1-ピラゾリル基、1,2,4-トリアゾール-1-イル基、1-テトラゾリル基などの含窒素ヘテロアリール基などを用いることができる。これらの含窒素ヘテロ環基は窒素以外のヘテロ原子、例えば酸素原子や硫黄原子を1個又は2個以上含んでいてもよい。また、含窒素ヘテロ環基は無置換であってもよいが、例えば、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、水酸基、ハロゲン原子、ハロゲン化 C_{1-6} アルキル基、カルボキシ基、 C_{1-6} アルコキシカルボニル基、 C_{1-6} アルキルカルボニル基、置換若しくは無置換のアミノ基などの置換基を1個または2個以上有していてもよい。含窒素ヘテロ環基と R^5 及び R^6 が結合する炭素原子との結合様式は特に限定されないが、含窒素ヘテロ環を構成する窒素原子と上記の炭素原子とが結合していることが好ましい。

R^7 は水素原子、1個又は2個以上の不飽和結合を有することもある C_{1-12} アルキル基、 C_{3-12} シクロアルキル基、 C_{4-12} シクロアルキル置換アルキル基、置換基を有することもあるアラルキル基、 C_{1-12} アルカノイル基、置換基を有することもあるアロイル基、又は置換基を有することもあるフェニル基を示す。 C_{1-12} アルキル基は直鎖若しくは分枝鎖のいずれであってもよく、1個又は2個以上の不飽和結

合を有していてもよい。不飽和結合として1個又は2個以上の二重結合と1個又は2個以上の三重結合とを組み合わせ有していてもよい。二重結合はZ-型又はE-型のいずれでもよい。 C_{3-12} シクロアルキル基としては、例えば、シクロプロピル基、シクロブチル基、シクロペンチル基、シクロヘキシル基などを用いることができるが、これらのシクロアルキル基はその環上に1個又は2個以上のアルキル基を有していてもよい。 C_{4-12} シクロアルキル置換アルキル基としては、上記のシクロアルキル基が置換したアルキル基、好ましくはシクロアルキル置換 C_{1-4} アルキル基、例えば、シクロプロピルメチル基などを用いることができる。

アラルキル基としては、例えば、ベンジル基、ナフチルメチル基、ビフェニルメチル基、フェネチル基などを挙げることができる。置換アラルキル基においてアリール環上に存在する1個又は2個以上の置換基としては、例えば、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、水酸基、ハロゲン原子、ハロゲン化 C_{1-6} アルキル基、カルボキシ基、 C_{1-6} アルコキシカルボニル基、 C_{1-6} アルキルカルボニル基、置換若しくは無置換のアミノ基などを用いることができる。

C_{1-12} アルカノイル基としては、例えば、アセチル基、プロパノイル基、ブタノイル基などを用いることができ、アロイル基としては、例えば、ベンゾイル基、ナフトイル基などを用いることができる。置換アロイル基においてアリール環上に存在する1個又は2個以上の置換基としては、例えば、 C_{1-6} アルキル基、 C_{1-6} アルコキシ基、水酸基、ハロゲン原子、ハロゲン化 C_{1-6} アルキル基、カルボキシ基、 C_{1-6} アルコキシカルボニル基、 C_{1-6} アルキルカルボニル基、置換若しくは無置換のアミノ基などを用いることができる。置換基を有するフェニル基の1又は2以上の置換基も上記の置換基から選択することができる。

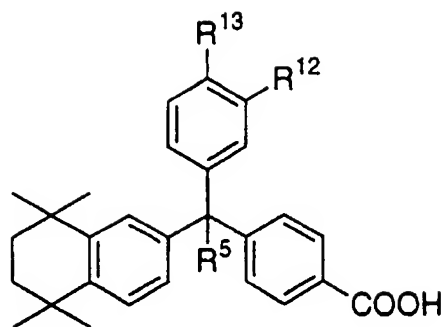
R^7 が置換基を有するフェニル基を示す場合、隣接した位置に2個の C_{1-6} アルキル基を有するフェニル基が好適であり、隣接する2個の C_{1-6} アルキル基が互いに結合して5ないし6員環、好ましくは6員環を形成していてもよい。このようにして形成される環は、その環上にさらに1個または2個以上の C_{1-4} アルキル基、好ましくは2～4個のメチル基、より好ましくは4個のメチル基を有していてもよい。例えば、 R^7 として5,6,7,8-テトラヒドロナフタレン-2-イル基、5,5,8,8-テトラメ

チル-5, 6, 7, 8- テトラヒドロナフタレン-2- イル基などを用いることができる。

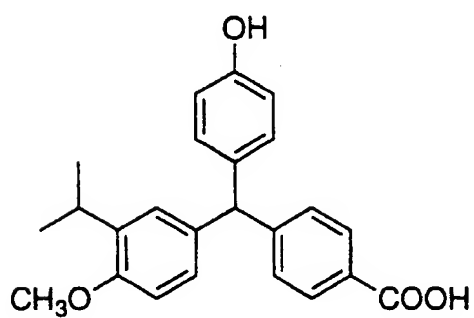
本発明の化合物には、酸付加塩または塩基付加塩が含まれる。酸付加塩としては、塩酸塩若しくは臭化水素酸塩などの鉱酸塩、又はp-トルエンスルホン酸塩、メタンスルホン酸塩、シュウ酸塩、若しくは酒石酸塩などの有機酸塩を挙げることができる。塩基付加塩としては、例えば、ナトリウム塩、カリウム塩、マグネシウム塩、若しくはカルシウム塩などの金属塩、アンモニウム塩、又はトリエチルアミン塩若しくはエタノールアミン塩などの有機アミン塩などを用いることができる。

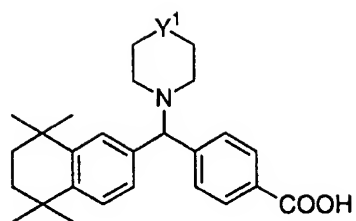
本発明の化合物は1個または2個以上の不斉炭素を有する場合があるが、このような不斉炭素に基づく任意の光学異性体、光学異性体の任意の混合物、ラセミ体、2個以上の不斉炭素に基づくジアステレオ異性体、ジアステレオ異性体の任意の混合物などは、いずれも本発明の範囲に包含される。また、1個又は2個以上の二重結合に基づく任意の幾何異性体も本発明の範囲に包含される。さらに、遊離化合物又は塩の形態の化合物の任意の水和物又は溶媒和物も本発明の範囲に包含される。

上記一般式(I)で示される本発明の化合物のうち、好ましい化合物の具体例を示すが、本発明の化合物は下記の化合物に限定されることはない。

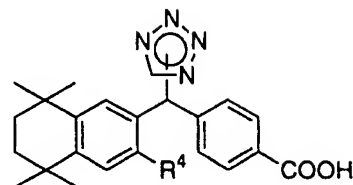
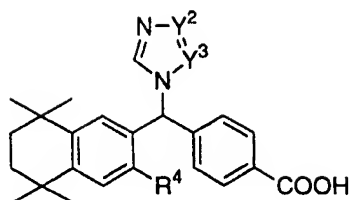


	R ⁵	R ¹²	R ¹³
DM010	H	H	H
DM011	H	H	OH
DM012	OH	H	H
DM013	H	H	OCH ₃
DM014	H	H	N(CH ₃) ₂
DM015	H	-OCH ₂ CH ₂ O-	
DM016	H	H	OCH ₂ CH ₂ -N

**DM040**

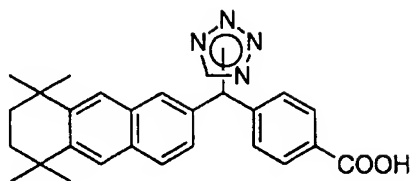


	Y ¹
DM020	CH ₂
DM021	O
DM022	NCH ₃

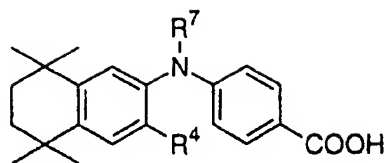


	R ⁴	Y ²	Y ³
DM030	H	C	N
DM032	H	C	C
DM130	CH ₃	C	N

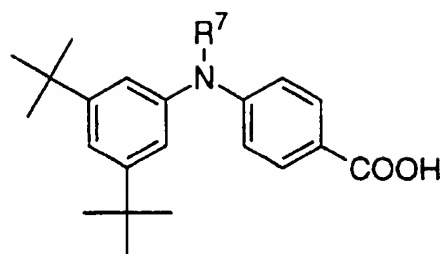
DM031 (TLC低極性異性体)
DM036 (TLC高極性異性体)



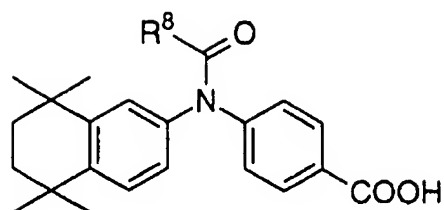
DM033 (TLC低極性異性体)



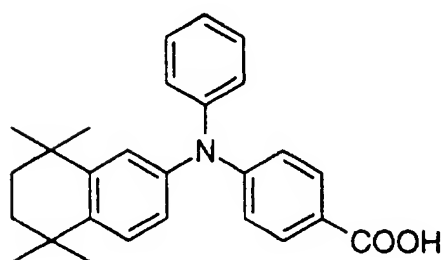
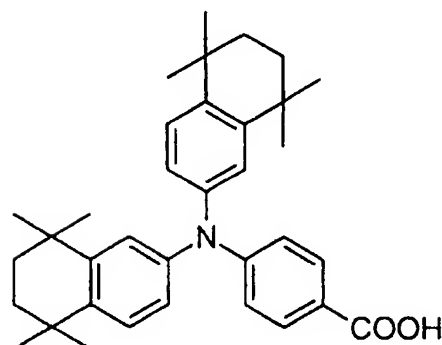
	R ⁴	R ⁷		R ⁴	R ⁷
DA010	H	H	DA040	H	CH ₂ C ₆ H ₅
DA011	H	CH ₃	DA041	H	CH ₂ C ₆ H ₄ - <i>p</i> -CH ₃
DA012	H	C ₂ H ₅	DA042	H	CH ₂ C ₆ H ₄ - <i>p</i> -CF ₃
DA013	H	<i>n</i> -C ₃ H ₇	DA045	H	CH ₂ C ₆ F ₄ - <i>p</i> -OC ₂ H ₅
DA014	H	<i>n</i> -C ₄ H ₉	DA046	H	CH ₂ C ₆ H ₄ - <i>o</i> -C ₆ H ₅
DA015	H	<i>n</i> -C ₅ H ₁₁	DA048	H	CH ₂ -2-C ₁₀ H ₇
DA016	H	<i>n</i> -C ₆ H ₁₃	DA112	CH ₃	C ₂ H ₅
DA017	H	<i>n</i> -C ₇ H ₁₅	DA113	CH ₃	<i>n</i> -C ₃ H ₇
DA018	H	<i>n</i> -C ₈ H ₁₇	DA114	CH ₃	<i>n</i> -C ₄ H ₉
DA020	H	CH ₂ C≡CH	DA120	CH ₃	CH ₂ C≡CH
DA021	H	CH ₂ CH=CH ₂	DA121	CH ₃	CH ₂ CH=CH ₂
DA022	H	<i>iso</i> -C ₃ H ₇	DA122	CH ₃	<i>iso</i> -C ₃ H ₇
DA023	H	<i>c</i> -C ₃ H ₅	DA123	CH ₃	<i>c</i> -C ₃ H ₇
DA024	H	CH ₂ (<i>c</i> -C ₃ H ₅)	DA124	CH ₃	CH ₂ (<i>c</i> -C ₃ H ₅)
DA025	H	CH ₂ CH(CH ₃) ₂	DA125	CH ₃	CH ₂ CH(CH ₃) ₂
DA028	H	CH ₂ CH=C(CH ₃) ₂	DA130	CH ₃	CH ₂ (<i>c</i> -C ₄ H ₇)
DA030	H	CH ₂ (<i>c</i> -C ₄ H ₇)	DA162	<i>n</i> -C ₃ H ₇	C ₂ H ₅
DA036	H	CH ₂ (<i>c</i> -C ₆ H ₁₁)	DA163	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇



	R^7
DA212	C_2H_5
DA213	$n-C_3H_7$
DA222	$iso-C_3H_7$
DA223	$c-C_3H_5$
DA224	$CH_2(c-C_3H_5)$
DA230	$CH_2(c-C_4H_7)$



	R^8
DA051	CH_3
DA055	C_6H_5
DA058	$C_6H_4-p-COOH$

**TA001****TA012**

本明細書の実施例には、本発明の式(1)に包含される上記の好ましい化合物の製造方法が具体的に説明されている。従って、これらの製造方法において用いられた出発原料及び試薬、並びに反応条件などを適宜修飾ないし改変することにより、本発明の範囲に包含される化合物はいずれも製造可能である。もっとも、本発明の化合物の製造方法は、実施例に具体的に説明されたものに限定されることはない。

上記式(1)で示される本発明の化合物はレチノイドの生理作用を調節する作用を有している。本明細書において「調節作用」という用語又はその類似語は、作

用の増強又は抑制を含めて最も広義に解釈する必要がある。本発明の化合物が増強作用又は抑制作用のいずれを有するかは、本明細書の試験例に具体的に示した方法に従って容易に検定可能である。

上記式(1)で示される本発明の化合物のうち、レチノイド作用増強性の化合物は、それ自体はレチノイド様の作用を実質的に有していないか、あるいは微弱又は中程度のレチノイド様作用を有しているが、本発明の化合物をレチノイン酸などのレチノイドと共存させた場合には、レチノイドの生理活性（代表的なものとして細胞分化作用、細胞増殖促進作用、及び生命維持作用など）を顕著に増強できるという特徴を有している。いかなる特定の理論に拘泥するわけではないが、本発明の化合物自体がレチノイド作用を有する場合には、その作用は相乗的作用である。

従って、レチノイン酸やレチノイン酸様の生物活性を有する化合物（例えば、4-[(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80など）を包含するレチノイドを、ビタミンA欠乏症；上皮組織の角化症、乾癬などの皮膚疾患；アレルギー疾患；リウマチなどの免疫性疾患；骨粗鬆症、骨折などの骨疾患；アルツハイマー；ハンチントン舞蹈病；白血病又は癌などの疾患の予防及び／又は治療のための医薬として投与する場合には、本発明の化合物を該レチノイドの作用増強剤として用いることができる。

また、レチノイドを上記疾患の治療及び／又は予防のために投与しない場合においても、本発明の化合物は生体内に既に存在するレチノイン酸の作用を増強するので、上記疾患の治療及び／又は予防の目的で本発明の化合物自体を投与することも可能である。さらに、本発明の化合物は、レチノイドに対しての作用増強効果のみならず、細胞の核内に存在する核内レセプター・スーパーファミリー (Evans, R. M., Science, 240, p. 889, 1988) に属するレセプター（核内レセプター）にリガンドとして結合して生理作用を発揮する生理活性物質、例えば、ステロイド化合物、ビタミンD₃などのビタミンD化合物、又はチロキシンなどの作用増強に用いることもできる。例えば、糖尿病、動脈硬化症、高脂血症、高コレステロール血症、骨疾患、リウマチ、又は免疫性疾患などの疾患の予防及び／又は

治療のための医薬として有用である。もっとも、本発明の化合物の用途は上記に具体的に説明した用途に限定されることはない。

また、上記式(I)で示される本発明の化合物のうち、レチノイド作用抑制性の化合物は、レチノイドの生理作用（代表的なものとして細胞分化作用、細胞増殖作用、及び生命維持作用など）を顕著に抑制する作用を有している。さらに、上記の化合物は、細胞の核内に存在する核内レセプター・スーパーファミリーに属するレセプターに結合して生理活性を発現する物質、例えば、ステロイド化合物、ビタミンD₃などのビタミンD化合物、又はチロキシンやリガンド不明のオーファンレセプターなどの作用を抑制することができる。従って、レチノイド作用抑制性の化合物は、例えば、これらの生理活性物質の作用発現の調節に用いることができ、核内レセプター・スーパーファミリーに属する核内レセプターの1又は2以上が関与する生物作用の異常を伴う疾患の予防及び／又は治療に用いることができる。

本発明の化合物を医薬として用いる場合には、上記一般式(I)の化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物から選ばれる1種または2種以上の物質をそのまま投与してもよいが、好ましくは、上記の物質の1種または2種以上を有効成分として含む経口用あるいは非経口用の医薬組成物を当業者に利用可能な製剤用添加物を用いて製造して投与することが好ましい。また、レチノイン酸などのレチノイドを有効成分として含む医薬に上記の物質の1種または2種以上を配合して、いわゆる合剤の形態の医薬組成物として用いることもできる。

経口投与に適する医薬用組成物としては、例えば、錠剤、カプセル剤、散剤、細粒剤、顆粒剤、液剤、及びシロップ剤等を挙げることができ、非経口投与に適する医薬組成物としては、例えば、注射剤、点滴剤、坐剤、吸入剤、点眼剤、点鼻剤、軟膏剤、クリーム剤、及び貼付剤等を挙げることができる。上記の医薬組成物の製造に用いられる薬理学的及び製剤学的に許容しうる製剤用添加物としては、例えば、賦形剤、崩壊剤ないし崩壊補助剤、結合剤、滑沢剤、コーティング剤、色素、希釈剤、基剤、溶解剤ないし溶解補助剤、等張化剤、pH調節剤、安定化

剤、噴射剤、及び粘着剤等を挙げることができる。

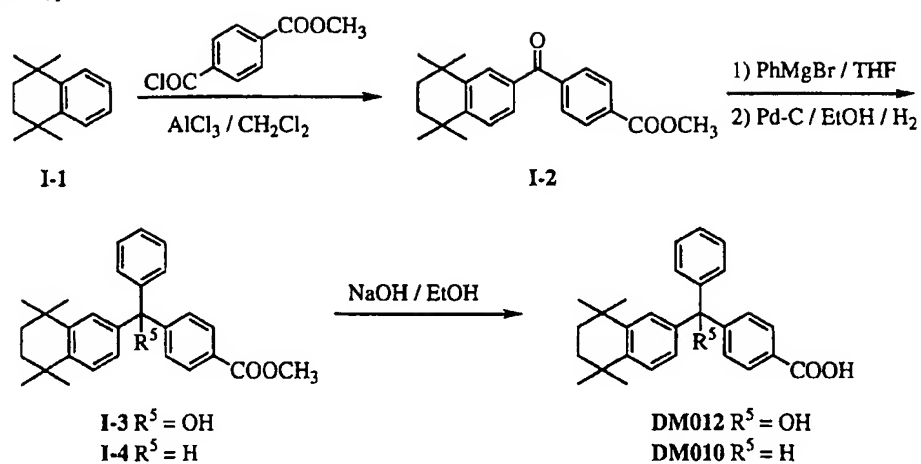
本発明の医薬の投与量は特に限定されず、レチノイン酸などのレチノイドを有効成分として含む医薬と本発明の医薬とを併用してレチノイドの作用を調節する場合、あるいは、レチノイドを含む医薬を併用せずに、生体内に既に存在するレチノイン酸の作用調節のために本発明の医薬を投与する場合など、あらゆる投与方法において適宜の投与量が容易に選択できる。例えば、経口投与の場合には成人一日あたり 0.01 ～1,000 mg程度の範囲で用いることができる。レチノイドを有効成分として含む医薬と本発明の医薬とを併用する場合には、レチノイドの投与期間中、及び／又はその前若しくは後の期間のいずれにおいても本発明の医薬を投与することが可能である。

実施例

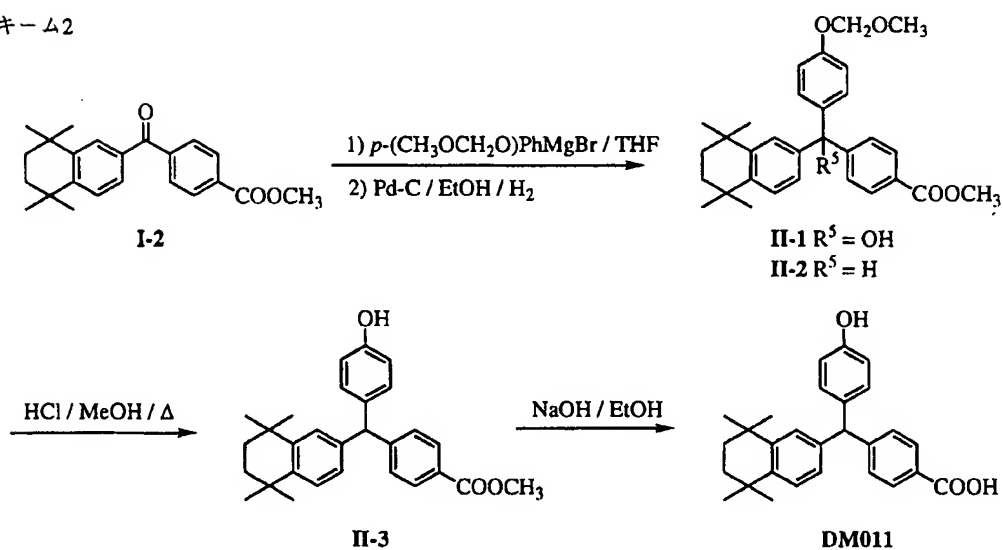
以下、本発明を実施例によりさらに具体的に説明するが、本発明の範囲は下記の実施例の範囲に限定されることはない。

以下の実施例で採用された製造方法をスキーム1からスキーム8に示す。スキーム中の化合物番号は、前記の好ましい化合物の化合物番号及び実施例中の化合物番号に対応している。

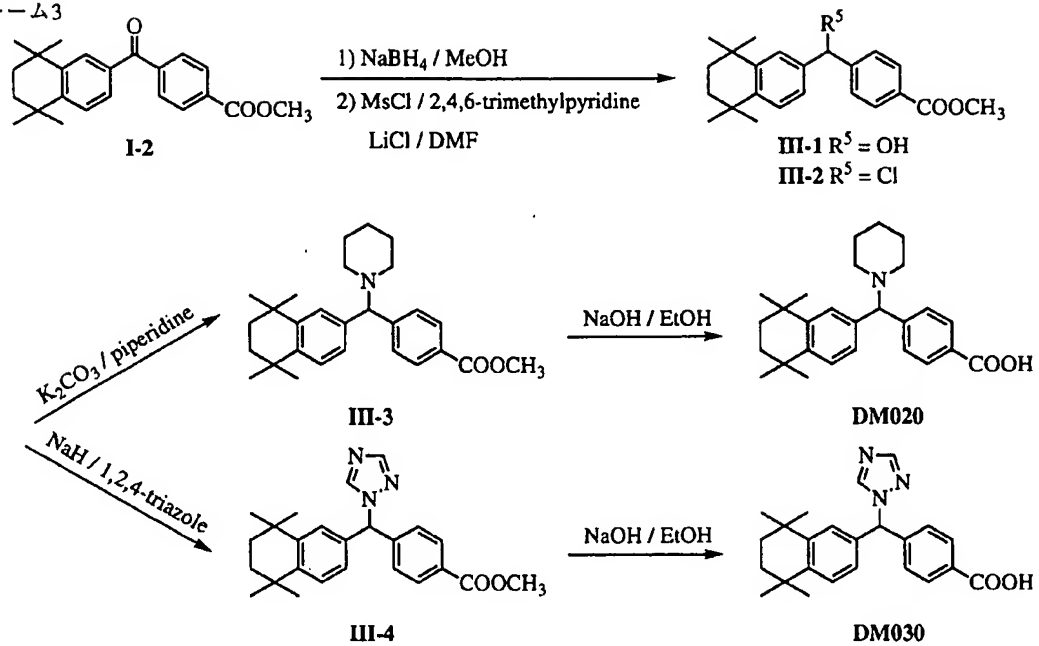
スキーム1



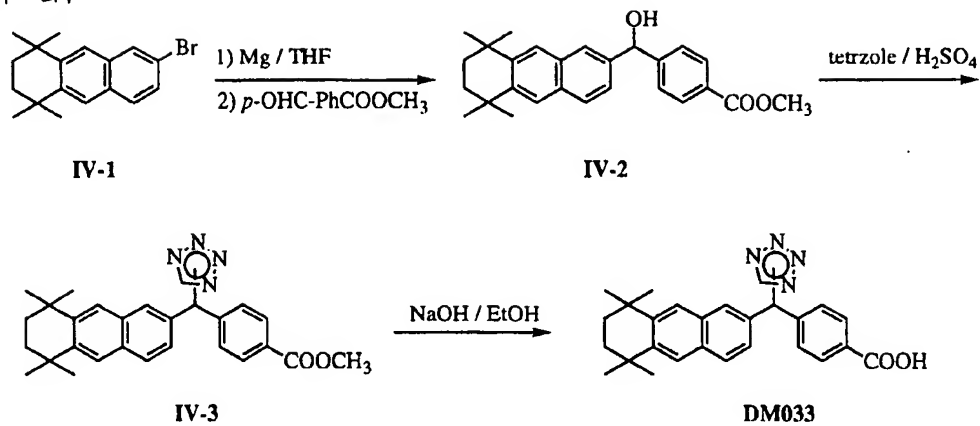
スキーム2



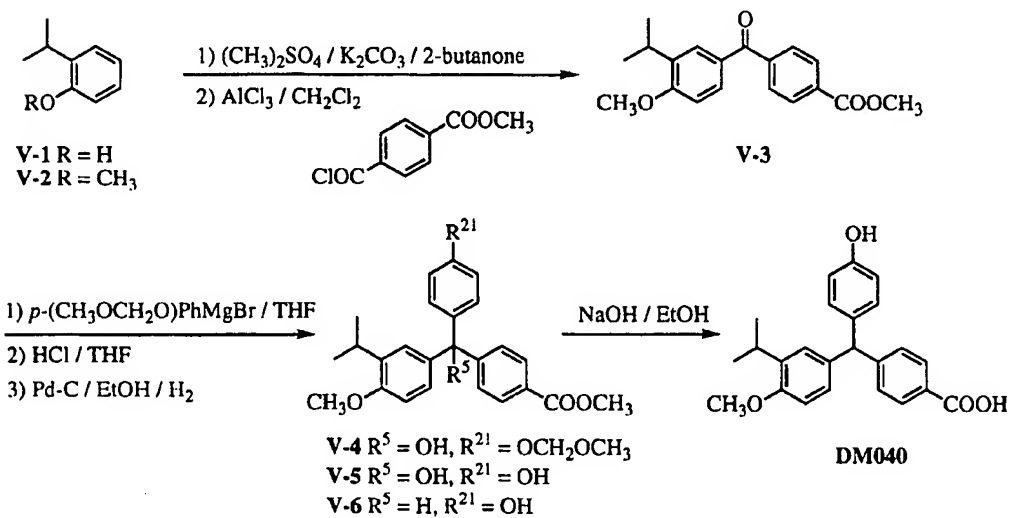
スキーム3



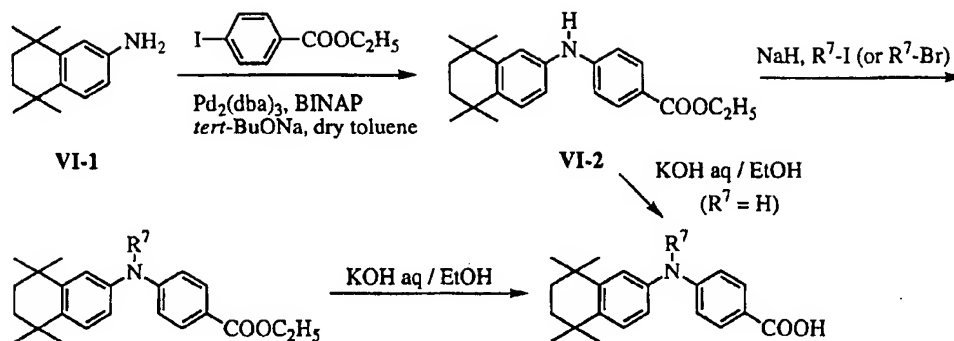
スキーム4



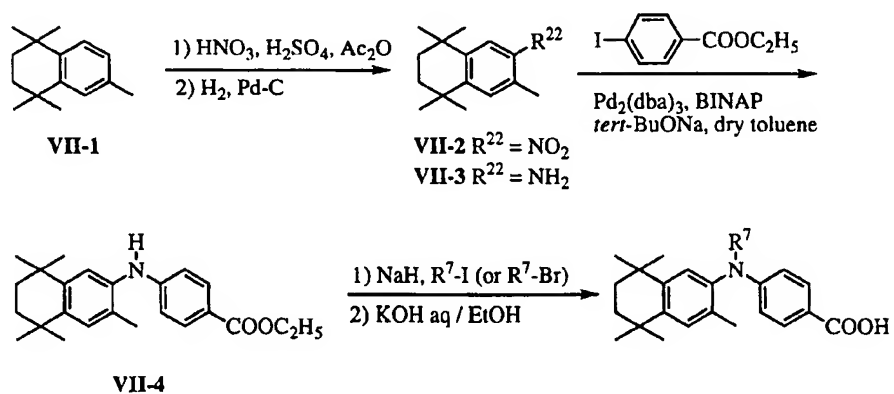
スキーム5



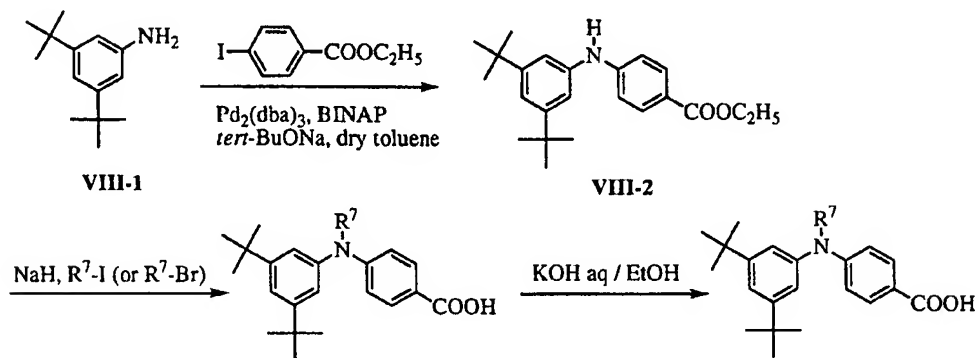
スキーム6



スキーム7



スキーム8



例1 : 4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) フェニルメチル] 安息香酸(DM010) の製造 (スキーム1)

5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン(I-1, 10.0 g) とモノメチルテレフタル酸クロライド (10.0 g) の塩化メチレン (100 ml) 溶液に、室温にて塩化アルミニウム (14.3 g) をゆっくりと加えた後、室温下で3時間攪拌した。反応混合物を氷を含む塩酸水溶液に注ぎ、クロロホルムで抽出した。減圧下で溶媒を留去し、残渣をシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 4 : 1) により精製し、4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) カルボニル] 安息香酸メチルエステル (化合物I-2, 11.2 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.15 (2H, d, $J=8$ Hz), 7.83 (2H, d, $J=8$ Hz), 7.79 (1H, d, $J=2$ Hz), 7.54 (1H, dd, $J=8, 2$ Hz), 7.41 (1H, d, $J=8$ Hz), 3.95 (3H, s), 1.73 (4H, s), 1.32 (6H, s), 1.29 (6H, s).

化合物I-2 (4.99 g) の無水THF 溶液 (30 ml) を窒素雰囲気下 0°C に冷却し、ブロモベンゼンのグリニャール溶液 (1M THF 溶液, 14.3 ml) をゆっくり滴下した。氷浴をはずして室温で40分間攪拌し、反応溶液を氷水中に注ぎ、酢酸エチルで抽出した。減圧下に溶媒を留去した後、残渣をシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 5 : 1) により精製し、4-[フェニル-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) ヒドロキシルメチル] 安息香酸メチルエステル(I-3, 4.45 g) を得た。

$^1\text{H-NMR}$ (90 MHz, CDCl_3) 7.96 (2H, d, $J=8$ Hz), 7.42 (2H, d, $J=8$ Hz), 7.37-6.81 (8H, m), 3.89 (3H, s), 2.85 (1H, s), 1.66 (4H, s), 1.27 (6H, s), 1.14 (6H, s).

化合物I-3 (4.0 g) のエタノール溶液 (220 ml) にPd-C (0.5 g) を加え、水素雰囲気下に室温で46時間攪拌した。反応液をセライトを通してろ過した後、減圧下に溶媒を留去した。得られた残渣を石油エーテルで再結晶して、4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) フェニルメチル] 安息香酸メチルエステル (I-4, 1.47 g) を得た。

$^1\text{H-NMR}$ (90 MHz, CDCl_3) 7.94 (2H, d, $J=8$ Hz), 7.44-6.69 (10H, m), 5.51 (1 H, s), 3.89 (3 H, s), 1.66 (4 H, s), 1.26 (6 H, s), 1.16 (6 H, s).

化合物I-4 (1.30 g)のエタノール溶液 (60 ml)に、3.5 M 水酸化ナトリウム水溶液 (4.5 ml)を加え、60℃で1.5 時間攪拌した。反応液を減圧下に濃縮し、残渣に水を加えて0 °Cに冷却しながら6 N 塩酸で酸性にした。析出した結晶をろ別し、乾燥後、石油エーテルで洗浄してDM010 (0.59 g)を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.98 (2H, d, $J=8$ Hz), 7.30-7.16 (6H, m), 7.09 (2H, d, $J=7$ Hz), 7.01 (1H, d, $J=2$ Hz), 6.79 (1H, dd, $J=8, 2$ Hz), 5.50 (1H, s), 1.65 (4H, s), 1.25 (6H, s), 1.16 (6H, s).

例2 : 4-[4- ヒドロキシフェニル-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) メチル] 安息香酸(DM011) の製造 (スキーム2)

氷冷下、化合物I-2 (8.10 g)の無水THF 溶液 (50 ml)に、別途調製した1-ブromo-4- メトキシメトキシベンゼン(5.0 g) のグリニャール溶液 (THF, 20 ml) をゆっくりと滴下した後、室温で2 時間攪拌した。反応溶液を氷水中に注ぎ、酢酸エチルで抽出し、減圧下に溶媒を留去した。残渣をシリカゲルクロマトグラフィー (n-ヘキサン : 酢酸エチル = 3 : 1)により精製し、化合物II-1 (7.50 g)を得た。

$^1\text{H-NMR}$ (90 MHz, CDCl_3) 7.97 (2H, d, $J=8$ Hz), 7.40 (2H, d, $J=8$ Hz), 7.3-6.8 (7H, m), 5.18 (2H, s), 3.90 (3H, s), 3.47 (3H, s), 2.75 (1H, s), 1.69 (4H, s), 1.25 (6H, s), 1.15 (6H, s).

化合物II-1 (1.81 g) のエタノール溶液 (100 ml) にPd-C (0.45 g)を加え、水素雰囲気下に室温で8.5 時間攪拌した。反応溶液をセライトを通してろ過した後、減圧下で溶媒を留去して化合物II-2 (0.76 g)を得た。

$^1\text{H-NMR}$ (90 MHz, CDCl_3) 7.93 (2H, d, $J=8$ Hz), 7.53-6.69 (7H, m), 7.18 (2H, d, $J=8$ Hz), 5.46 (1H, s), 5.15 (2H, s), 3.89 (3H, s), 3.47 (3H, s), 1.66 (4H, s), 1.26 (6H, s), 1.16 (6H, s).

化合物II-2 (0.75 g) のメタノール溶液 (60 ml)に、濃塩酸2 滴を加え、40-50 °Cに加熱して9.5 時間攪拌した。反応溶液を減圧下に濃縮し、残渣をシリカゲル

カラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 3 : 1) により精製し、化合物II-3 (0.63 g) を得た。

$^1\text{H-NMR}$ (90 MHz, CDCl_3) 7.93 (2H, d, $J=8$ Hz), 7.37-6.62 (9H, m), 5.44 (1H, s), 5.20 (1H, br s), 3.89 (3H, s), 1.65 (4H, s), 1.25 (6H, s), 1.16 (6H, s).

化合物II-3 (0.60 g) のエタノール溶液 (10 ml) に、2.7 N 水酸化ナトリウム水溶液 (2 ml) を加え、60°C で2時間攪拌した。反応溶液を減圧下濃縮し、残渣に水を加え、0 °C に冷却しながら6 N 塩酸を加えて混合物を酸性にした。析出した結晶をろ別し、水でよく洗浄した後、減圧下で乾燥した。この結晶をジエチルエーテル-石油エーテルから再結晶してDM011 (0.40 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.01 (2H, d, $J=8$ Hz), 7.22 (2H, d, $J=8$ Hz), 7.19 (1H, d, $J=8$ Hz), 7.00 (1H, d, $J=2$ Hz), 6.97 (2H, d, $J=8$ Hz), 6.79 (1H, dd, $J=8, 2$ Hz), 6.76 (2H, d, $J=8$ Hz), 5.46 (1H, s), 1.66 (4H, s), 1.23 (6H, s), 1.16 (6H, s).

例3 : 4-[フェニル-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) ヒドロキシメチル] 安息香酸(DM012) の製造 (スキーム1)

化合物I-3 (2.0 g) のエタノール溶液 (30 ml) に、水酸化ナトリウム (0.60 g) の水溶液 (5 ml) を加え、約50°C で3時間攪拌した。反応液を減圧下濃縮し、残渣に水を加え、塩酸水溶液で酸性にした。析出した結晶をろ別し、乾燥後、石油エーテルで洗浄してDM012 (1.2 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.88 (2H, d, $J=8$ Hz), 7.38-7.20 (8H, m), 7.15 (1H, d, $J=2$ Hz), 6.89 (1H, d, $J=8, 2$ Hz), 6.46 (1H, s), 1.65 (4H, s), 1.22 (6H, s), 1.10 (6H, s).

例4 : 4-[4-メトキシフェニル-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) メチル] 安息香酸 (DM013) の製造

化合物I-2(例1参照) とp-ブロモアニソールを出発原料とし、例1に記載の方

法に従い、DM013 を得た。

^1H -NMR (400 MHz, CDCl_3) 12.82 (1H, br s), 7.87 (2H, d, $J=8$ Hz), 7.24-7.18 (3H, m), 7.07 (1H, s), 7.03 (2H, d, $J=8$ Hz), 6.88 (2H, d, $J=8$ Hz), 6.83 (1H, d, $J=8$ Hz), 5.54 (1H, s), 3.72 (3H, s), 1.61 (4H, s), 1.21 (6H, s), 1.14 (3H, s), 1.13 (3H, s).

例5 : 4-[4-ジメチルアミノフェニル-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)メチル]安息香酸(DM014)の製造

化合物I-2 と4-ブromo-N,N-ジメチルアニリンを出発原料とし、例1に記載の方法に従い、DM014 を得た。

^1H -NMR (400 MHz, CDCl_3) 8.00 (2H, d, $J=8$ Hz), 7.24 (2H, d, $J=8$ Hz), 7.18 (1H, d, $J=8$ Hz), 7.03 (1H, d, $J=2$ Hz), 6.97 (2H, d, $J=9$ Hz), 6.81 (1H, dd, $J=8, 2$ Hz), 6.68 (2H, d, $J=9$ Hz), 5.43 (1H, s), 2.92 (6H, s), 1.65 (4H, s), 1.25 (6H, s), 1.17 (3H, s), 1.16 (3H, s).

例6 : 4-[3,4-メチレンジオキシフェニル-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)メチル]安息香酸 (DM015)の製造

化合物I-2 と4-ブromo-1,2-(メチレンジオキシ)ベンゼンを出発原料とし、例1に記載の方法に従い、DM015 を得た。

^1H -NMR (400 MHz, CDCl_3) 8.01 (2H, d, $J=8$ Hz), 7.23 (2H, d, $J=8$ Hz), 7.20 (1H, d, $J=8$ Hz), 7.01 (1H, d, $J=2$ Hz), 6.80 (1H, dd, $J=8, 2$ Hz), 6.73 (1H, d, $J=8$ Hz), 6.59 (1H, d, $J=2$ Hz), 6.57 (1H, dd, $J=8, 2$ Hz), 5.93 (2H, s), 5.44 (1H, s), 1.66 (4H, s), 1.26 (6H, s), 1.18 (3H, s), 1.17 (3H, s).

例7 : 4-[4-[2-(1-ピロリジニル)エトキシ]フェニル-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)メチル]安息香酸 (DM016)の製造

化合物I-2 と1-[2-(4-ブromoフェノキシ)エチル]ピロリジンを出発原料とし、例1に記載の方法に従ってDM016 を得た。

^1H -NMR (400 MHz, CDCl_3 + DMSO-d_6) 12.28 (1H, br s), 7.94 (2H, d, $J=8$ Hz), 7.18 (1H, d, $J=8$ Hz), 7.17 (2H, d, $J=8$ Hz), 7.03 (2H, d, $J=9$ Hz), 7.01 (1H, d, $J=2$ Hz), 6.85 (2H, d, $J=9$ Hz), 6.78 (1H, dd, $J=8, 2$ Hz), 5.45 (1H, s), 4.48 (2H, t, $J=5$ Hz), 3.76 (2H, br s), 3.54 (1H, t, $J=5$ Hz), 3.11 (2H, br s), 2.14 (4H, br s), 1.66 (4H, s), 1.25 (6H, s), 1.17 (3H, s), 1.16 (3H, s).

例 8 : 4-[(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン2-イル) ピペリジノメチル] 安息香酸(DM020) の製造 (スキーム 3)

化合物I-2 (5.0 g) のメタノール溶液 (200 ml) に、室温下で水素化ホウ素ナトリウム (0.60 g) をゆっくり加えた後、混合物を更に 2 時間攪拌した。反応混合物を氷水中に注ぎ、析出した結晶をろ別し、十分に水洗して化合物III-1 (5.10 g) を得た。

^1H -NMR (400 MHz, CDCl_3) 7.90 (2H, d, $J=8$ Hz), 7.47 (2H, d, $J=8$ Hz), 7.29 (1H, d, $J=2$ Hz), 7.25 (1H, d, $J=8$ Hz), 7.04 (1H, dd, $J=8, 2$ Hz), 5.82 (1H, d, $J=3$ Hz), 3.89 (3H, s), 2.34 (1H, d, $J=3$ Hz), 1.66 (4H, s), 1.23-1.26 (12H, m).

化合物III-1 (5.10 g)、2,4,6-トリメチルピリジン(2.1 g)、リチウムクロライド(0.74 g)の無水ジメチルホルムアミド(DMF) 溶液(30 ml) に、室温下でメタンスルフォニルクロライド(2.0 g) をゆっくりと加えた後、反応混合物を徐々に加温して約50℃で 3 時間攪拌した。反応混合物を氷水中に注ぎ、酢酸エチルで抽出した後、有機相を減圧濃縮した。残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 4 : 1) で精製して化合物III-2 (2.4 g) を得た。

^1H -NMR (400 MHz, CDCl_3) 8.02 (2H, d, $J=8$ Hz), 7.51 (2H, d, $J=8$ Hz), 7.30 (1H, d, $J=2$ Hz), 7.26 (1H, d, $J=8$ Hz), 7.09 (1H, dd, $J=8, 2$ Hz), 6.11 (1H, s), 3.91 (3H, s), 1.67 (4H, s), 1.26 (6H, s), 1.23 (6H, s).

化合物III-2 (1.001 g)、ピペリジン(0.691 g)、炭酸カリウム(1.175 g) の無水DMF 溶液(10 ml) を約90℃にて 3 時間攪拌した。反応溶液を冷却して氷水中に

注ぎ、酢酸エチルで抽出した。減圧下に溶媒を留去し、残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 8 : 1) により精製し、化合物III-3 (0.844 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.93 (2H, d, $J=8$ Hz), 7.48 (2H, d, $J=8$ Hz), 7.28 (1H, d, $J=2$ Hz), 7.14 (1H, d, $J=8$ Hz), 7.03 (1H, dd, $J=8, 2$ Hz), 4.21 (1H, s), 3.87 (3H, s), 2.23 (4H, m), 1.62 (4H, s), 1.55 (4H, m), 1.42 (2H, m), 1.23 (6H, s), 1.21 (6H, s).

上記エステル(0.844 g) のエタノール溶液(10 ml) に5 N 水酸化ナトリウム水溶液 (1.2 ml) を加えて50℃で1時間攪拌した。反応混合物を減圧下濃縮し、残査に水を加えて0 °Cに冷却しながら塩酸水溶液で中和した。混合物を酢酸エチルで抽出し、有機相を減圧濃縮して得られた残査を石油エーテルで再結晶し、DM020 (0.756 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.08 (2H, d, $J=8$ Hz), 7.64 (2H, d, $J=8$ Hz), 7.40 (1H, d, $J=2$ Hz), 7.20 (1H, dd, $J=8, 2$ Hz), 7.17 (1H, d, $J=8$ Hz), 4.47 (1H, s), 2.59 (4H, m), 1.70 (4H, m), 1.61 (4H, s), 1.48 (2H, m), 1.21 (6H, s), 1.19 (6H, s).

例9 : 4-[(5,6,7,8-テトラヒドロ-5,5,8,8テトラメチルナフタレン-2-イル) モルホリノメチル] 安息香酸(DM021) の製造

化合物III-2 とモルフォリンを出発原料とし、例8に記載の方法に従い、DM021を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.01 (2H, d, $J=8$ Hz), 7.55 (2H, d, $J=8$ Hz), 7.30 (1H, d, $J=2$ Hz), 7.17 (1H, d, $J=8$ Hz), 7.08 (1H, dd, $J=8, 2$ Hz), 4.22 (1H, s), 3.72 (4H, m), 2.38 (4H, m), 1.62 (4H, s), 1.24 (3H, s), 1.23 (3H, s), 1.21 (6H, s).

例10 : 4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル)-
(4- メチルピペラジン-1- イル) メチル] 安息香酸(DM022) の製造

化合物III-2 と1-メチルピペラジンを出発原料として、例8に記載の方法に従い、DM022 を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.92 (2H, d, $J=8$ Hz), 7.37 (2H, d, $J=8$ Hz), 7.27 (1H, d, $J=1.5$ Hz), 7.15 (1H, d, $J=8$ Hz), 7.08 (1H, dd, $J=8, 1.5$ Hz), 4.32 (1H, s), 2.87 (4H, br s), 2.55 (4H, br s), 2.52 (3H, s), 1.62 (4H, s), 1.21 (12H, s).

例11 : 4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル)-
(1, 2, 4- トリアゾール-1- イル) メチル] 安息香酸(DM030) の製造 (スキーム3)

乾燥窒素雰囲気下で水素化ナトリウム (油中60%, 0.11 g)の無水DMF (20 ml) 溶液に1, 2, 4-トリアゾール (0.17 g) を室温下に加え、約1時間攪拌した後、化合物III-2 (1.0 g) を加えた。この反応液を徐々に加熱し、約80℃で5時間攪拌した。反応混合物を冷却して氷水中に注ぎ酢酸エチルで抽出した。有機相を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル) により精製して化合物III-4 (0.81 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.05 (2H, d, $J=8$ Hz), 8.04 (1H, s), 7.92 (1H, s), 7.28 (1H, d, $J=8$ Hz), 7.18 (2H, d, $J=8$ Hz), 7.10 (1H, d, $J=2$ Hz), 6.90 (1H, dd, $J=8, 2$ Hz), 6.73 (1H, s), 3.92 (3H, s), 1.67 (4H, s), 1.26 (6H, s), 1.20 (3H, s), 1.17 (3H, s).

化合物III-4 (0.80 g)のエタノール溶液(10 ml) に水酸化ナトリウム(0.24 g) の水溶液 (3 ml) を加え、この混合物を約50℃で3時間攪拌した。反応溶液を減圧下に濃縮し、残渣に水を加えて塩酸水溶液でpH 6とした後、混合物を酢酸エチルで抽出した。有機相を減圧濃縮し、残渣を石油エーテルで洗浄してDM030 (0.53 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.09 (2H, d, $J=8$ Hz), 8.07 (1H, s), 7.98 (1H, s),

7.30 (1H, d, J=8 Hz), 7.19 (2H, d, J=8 Hz), 7.12 (1H, d, J=2 Hz), 6.89 (1H, d, J=8, 2 Hz), 6.75 (1H, s), 1.68 (4H, s), 1.27 (3H, s), 1.26 (3H, s), 1.21 (3H, s), 1.17 (3H, s).

例12: 4-[(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル)- テトラゾイルメチル] 安息香酸(DM031およびDM036) の製造

化合物III-1 (3.0 g) の酢酸懸濁液 (50 ml) に 1H-テトラゾール(1.87 g)、濃硫酸5滴を加えて室温で24時間攪拌した。反応液を氷水中に注ぎ、水酸化ナトリウム水溶液中で中和し、酢酸エチルで抽出した。減圧下に溶媒を留去し、残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン:クロロホルム=1:1ついで0:1)により精製して、4-[(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル)-テトラゾイルメチル] 安息香酸メチルエステルの2種の異性体(TLC低極性エステル 0.810 gおよびTLC 高極性エステル 1.50 g)を得た。

低極性エステル: $^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.57 (1H, s), 8.03 (2H, d, J=8 Hz), 7.31 (2H, d, J=8 Hz), 7.31 (1H, s), 7.29 (1H, d, J=8 Hz), 7.19 (1H, d, J=2 Hz), 7.01 (1H, dd, J=8, 2 Hz), 3.91 (3H, s), 1.66 (4H, s), 1.25 (6H, s), 1.19 (3H, s), 1.18 (3H, s).

高極性エステル: $^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.44 (1H, s), 8.06 (2H, d, J=8.5 Hz), 7.32 (1H, d, J=8 Hz), 7.15 (2H, d, J=8 Hz), 7.10 (1H, d, J=2 Hz), 7.05 (1H, s), 6.87 (1H, dd, J=8, 2 Hz), 3.93 (3H, s), 1.68 (4H, s), 1.27 (6H, s), 1.21 (3H, s), 1.16 (3H, s)

上記低極性エステル (0.622 g) のエタノール溶液 (10 ml) に 5 N 水酸化ナトリウム水溶液 (1 ml) を加え、50℃で3時間攪拌した。反応混合物を減圧濃縮し、残査に水を加えて0℃に冷却しなから塩酸水溶液を加えて酸性とした。この混合物を酢酸エチルで抽出して有機相を減圧濃縮し、得られた残査を石油エーテルで再結晶して、DM031 (0.226 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.59 (1H, s), 8.10 (2H, d, J=8 Hz), 7.35 (2H, d, J=8 Hz), 7.33 (1H, s), 7.30 (1H, d, J=8 Hz), 7.21 (1H, d, J=2 Hz), 7.03

(1H, dd, J=8, 2 Hz), 1.66 (4H, s), 1.26 (6H, s), 1.20 (3H, s), 1.19 (3H, s).

上記高極性エステル(1.40 g)を同様にして加水分解することによりDM036 (1.10 g)を得た。

$^1\text{H-NMR}$ (400 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) 8.57 (1H, s), 8.07 (2H, d, J=8 Hz), 7.32 (1H, d, J=8 Hz), 7.17 (2H, d, J=8 Hz), 7.11 (1H, d, J=2 Hz), 7.09 (1H, s), 6.89 (1H, dd, J=8, 2 Hz), 1.68 (4H, s), 1.27 (6H, s), 1.21 (3H, s), 1.17 (3H, s).

例13: 4-[(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)-(イミダゾール-1-イル)メチル]安息香酸(DM032)の製造

化合物III-2 とイミダゾールを出発原料とし、例11に記載の方法に従い、DM032を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.95 (2H, d, J=8 Hz), 7.66 (1H, s), 7.33 (1H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz), 7.12 (2H, br s), 6.97 (1H, s), 6.90 (1H, dd, J=8, 2 Hz), 6.87 (1H, s), 1.63 (4H, s), 1.22 (6H, s), 1.16 (3H, s), 1.14 (3H, s).

例14: 4-[(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルアントラセン-2-イル)-テトラゾイル]メチル]安息香酸(DM033)の製造(スキーム4)

p-ホルミル安息香酸メチルエステル (6.2 g)の無水THF 溶液 (30 ml)に、別途調製した2-ブロモ-5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルアントラセン(IV-1, 10 g)のグリニャール溶液 (THF, 30 ml)を氷冷下に約1時間かけて滴下した。反応混合物を室温で2時間攪拌した後、氷水中に注いで酢酸エチルで抽出した。有機相を減圧濃縮し、残渣をシリカゲルカラムクロマトグラフィー (n-ヘキサン:酢酸エチル = 3:1)により精製して化合物IV-2 (6.5 g)を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.98 (2H, d, J=8 Hz), 7.75 (2H, d, J=8 Hz), 7.73 (1H, d, J=2 Hz), 7.68 (1H, d, J=8 Hz), 7.48 (2H, d, J=8 Hz), 7.26 (1H,

dd, J=8, 2 Hz), 5.98 (1H, d, J=3 Hz), 3.88 (3H, s), 2.42 (1H, d, J=3 Hz), 1.76 (4H, s), 1.38 (6H, s), 1.37 (6H, s).

化合物IV-2 (0.502 g)の酢酸溶液 (2 ml) に 1H-テトラゾール (0.131 g)、濃硫酸 1 滴を加えて室温で17時間攪拌した。反応溶液を氷水中に注ぎ、析出してきた固体をろ過して乾燥した後、シリカゲルカラムクロマトグラフィー (n-ヘキサン：酢酸エチル= 5 : 1)により精製し、化合物IV-3 (TLC 低極性異性体、0.212 g)を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.60 (1H, s), 8.04 (2H, d, J=8 Hz), 7.77 (1H, s), 7.74 (1H, d, J=8 Hz), 7.71 (1H, s), 7.56 (1H, d, J=2 Hz), 7.50 (1H, s), 7.33 (2H, d, J=8 Hz), 7.26 (1H, dd, J=8, 2 Hz), 3.91 (3H, s), 1.75 (4H, s), 1.37 (6H, s), 1.36 (6H, br s).

化合物IV-3 (0.197 g)のエタノール (5 ml) 溶液に5 N 水酸化ナトリウム水溶液(0.5 ml)を加え、50℃で3時間攪拌した。反応混合物を減圧濃縮し、残査に水を加えて0℃に冷却しながら塩酸水溶液を加えて酸性とした。混合物を酢酸エチルで抽出し、得られた残査を石油エーテルで再結晶して、DM033 (0.190 g)を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.60 (1H, s), 8.06 (2H, d, J=8 Hz), 7.77 (1H, s), 7.74 (1H, d, J=8 Hz), 7.71 (1H, s), 7.56 (1H, d, J=2 Hz), 7.51 (1H, s), 7.31 (2H, d, J=8 Hz), 7.26 (1H, dd, J=8, 2 Hz), 1.75 (4H, s), 1.37 (6H, s), 1.36 (6H, br s).

例15： 4-[4-ヒドロキシフェニル-(3-イソプロピル-4-メトキシフェニル)メチル]安息香酸(DM040)の製造 (スキーム5)

アルゴン雰囲気下、o-イソプロピルフェノール(V-1, 25.67 g)、炭酸カリウム (77.32 g)の無水2-ブタノン溶液 (300 ml) に、ジメチル硫酸 (27 ml)をゆっくり滴下した後、約70℃で10時間攪拌した。反応溶液を冷却後に濾過して、濾液を減圧濃縮し、得られた残査に1 N 水酸化ナトリウム水溶液(150 ml)を加えた。混合物を室温で12時間攪拌した後、ジクロロメタンで抽出した。有機相を減圧濃縮し、得られた残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン：酢酸エチル=

7 : 1)により精製して、化合物V-2 (25.94 g) を油状物として得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.21 (1H, dd, $J=7.5, 1.7$ Hz), 7.15 (1H, ddd, $J=8, 7.5, 1.7$ Hz), 6.92 (1H, ddd, $J=7.5, 7.5, 1$ Hz), 6.84 (1H, dd, $J=8, 1$ Hz), 3.82 (3H, s), 3.32 (1H, m, $J=7$ Hz), 1.21 (6H, d, $J=7$ Hz).

化合物V-2 (17.23 g)、モノメチルテレフタル酸クロリド (25.44 g)の無水ジクロロメタン溶液 (300 ml) に、水冷下で塩化アルミニウム (23.61 g) をゆっくり加え、この混合物を室温で18時間攪拌した。反応混合物を氷を含む塩酸水溶液中に注ぎ、ジクロロメタンで抽出した。減圧下に溶媒を留去し、残査をn-ヘキサンから再結晶して化合物V-3 (23.31 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.14 (2H, d, $J=8.6$ Hz), 7.80-7.78 (3H, m), 7.63 (1H, dd, $J=8.5, 2.5$ Hz), 6.88 (1H, d, $J=8.5$ Hz), 3.96 (3H, s), 3.91 (3H, s), 3.34 (1H, m, $J=7$ Hz), 1.21 (6H, d, $J=7$ Hz).

化合物V-3 (2.0 g) の無水THF 溶液 (25 ml) に、別途調製した1-ブロモ-4-メトキシメトキシベンゼン (1.52 g) のグリニャール溶液 (THF, 6 ml) を水冷下でゆっくりと滴下した後、混合物を室温で1時間攪拌した。反応液を氷水中に注ぎ、酢酸エチルで抽出して減圧下に溶媒を留去し、残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 5 : 1 ~ 3 : 1) で精製して化合物V-4 (0.88 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.96 (2H, d, $J=8.8$ Hz), 7.40 (2H, d, $J=8.8$ Hz), 7.16 (2H, d, $J=8.8$ Hz), 7.13 (1H, d, $J=2.4$ Hz), 6.95 (2H, d, $J=8.8$ Hz), 6.91 (1H, dd, $J=8.8, 2.4$ Hz), 6.73 (1H, d, $J=8.8$ Hz), 5.15 (2H, s), 3.89 (3H, s), 3.80 (3H, s), 3.46 (3H, s), 3.26 (1H, m, $J=7$ Hz), 2.85 (1H, s), 1.11 (6H, d, $J=7$ Hz).

化合物V-4 (0.80 g) のTHF 溶液 (10 ml) に濃塩酸 (3 滴) を加え、約50°Cで5時間攪拌した。反応溶液を冷却し、水を加えて酢酸エチルで抽出した。有機相を減圧濃縮し、得られた残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 2 : 1) で精製して化合物V-5 (0.49 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.95 (2H, d, $J=8.7$ Hz), 7.39 (2H, d, $J=8.7$ Hz),

7.79 (1H, d, J=2.5 Hz), 7.08 (2H, d, J=8.8 Hz), 6.90 (1H, dd, J=8.5, 2.5 Hz), 6.76 (2H, d, J=8.8 Hz), 6.73 (1H, d, J=8.5 Hz), 5.68 (1H, s), 3.90 (3H, s), 3.80 (3H, s), 3.25 (1H, m, J=7 Hz), 2.85 (1H, s), 1.10 (6H, d, J=7 Hz).

化合物V-5 (0.14 g)のエタノール溶液 (13 ml)に Pd-C (0.05 g)を加え、水素雰囲気下で2時間攪拌した。活性炭を通して反応溶液を濾過し、減圧下に溶媒を留去した。残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン:酢酸エチル = 2:1)により精製して化合物V-6 (0.11 g)を得た。

¹H-NMR (400 MHz, CDCl₃) 7.94 (2H, d, J=8.5 Hz), 7.18 (2H, d, J=8.5 Hz), 6.94 (3H, m), 6.72 (1H, dd, J=8.3, 2.4 Hz), 6.75 (2H, d, J=8.5 Hz), 6.74 (1H, d, J=8.5 Hz), 5.46 (1H, s), 5.25 (1H, s), 3.89 (3H, s), 3.76 (3H, s), 3.25 (1H, m, J=7 Hz), 1.12 (6H, d, J=7 Hz).

化合物V-6 (0.06 g)のエタノール溶液 (7 ml)に1 N 水酸化ナトリウム水溶液 (1 ml)を加え、約50℃で6時間攪拌した後、反応液を減圧濃縮した。残査に水を加え、0℃に冷却しながら塩酸水溶液を加えて酸性とした後、酢酸エチルで抽出した。得られた残査をジエチルエーテル-石油エーテルで再結晶してDM040 (0.04 g)を得た。

¹H-NMR (400 MHz, CDCl₃) 7.94 (2H, d, J=8.3 Hz), 7.17 (2H, d, J=8.3 Hz), 6.95 (1H, d, J=2.5 Hz), 6.90 (2H, d, J=8.5 Hz), 6.81 (1H, dd, J=8.5, 2.5 Hz), 6.76 (2H, d, J=8.5 Hz), 6.73 (1H, d, J=8.5 Hz), 5.43 (1H, s), 3.79 (3H, s), 3.24 (1H, m, J=7 Hz), 1.12 (6H, d, J=7 Hz).

例16: 4-[(5,6,7,8-テトラヒドロ-3,5,5,8,8-ペンタメチルナフタレン-2-イル)-(1,2,4-トリアゾル-1-イル)メチル]安息香酸 (DM130)の製造

4-[(5,6,7,8-テトラヒドロ-3,5,5,8,8-ペンタメチルナフタレン-2-イル)カルボニル]安息香酸メチルエステル (5.0 g)をテトラヒドロフラン(250 ml)とメタノール(100 ml)の混合溶液に溶解し、室温にて、原料が消失するまで水素化ホウ素ナトリウムを加える。原料消失後、反応混合物を氷水中に注ぎ、エーテルで抽

出した。有機相を減圧濃縮することにより、定量的に還元体を得た。これをテトラヒドロフラン(250 ml)に溶解し、水冷下、塩酸ガスを吹き込みながら、24時間攪拌した。反応混合物を減圧下濃縮し、残渣をn-ヘキサンより再結晶を繰り返すことにより、4-[(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8-ペンタメチルナフタレン-2-イル)クロロメチル]安息香酸メチルエステル(4.0 g)の結晶を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.02 (2H, d, $J=8$ Hz), 7.47 (2H, d, $J=8$ Hz), 7.30 (1H, s), 7.07 (1H, s), 6.30 (1H, s), 3.91 (3H, s), 2.27 (3H, s), 1.65 (4H, s), 1.27 (3H, s), 1.26 (3H, s), 1.25 (3H, s), 1.15 (3H, s).

4-[(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8-ペンタメチルナフタレン-2-イル)クロロメチル]安息香酸メチルエステルと1, 2, 4-トリアゾールを出発原料とし、例11に記載の方法に従い、DM130を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 8.11 (2H, d, $J=8$ Hz), 8.08 (1H, s), 7.84 (1H, s), 7.14 (1H, s), 7.12 (2H, d, $J=8$ Hz), 6.93 (1H, s), 6.67 (1H, s), 2.17 (3H, s), 1.62 (4H, br s), 1.27 (3H, s), 1.27 (3H, s), 1.08 (3H, s), 1.01 (3H, s).

例17: 4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8-テトラメチルナフタレン-2-イル)アミノ]安息香酸(DA010)の製造(スキーム6)

6-アミノ-1, 2, 3, 4-テトラヒドロ-1, 1, 4, 4-テトラメチルナフタレン(VI-1, 1.214 g, 5.97 mmol)、4-ヨード安息香酸エチル(1.622 g, 5.87 mmol)及びtert-BuONa(600 mg)を無水トルエン 60 mlに溶かし、アルゴン置換下、トリス(ジベンジリデンアセトン)ジパラジウム(0) 97.0 mg、(R)-BINAP 158 mgを入れ、80℃で加熱した。1時間後、室温まで冷やし、水 200 ml にあけエーテルで抽出した。有機層を硫酸マグネシウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー(n-ヘキサン:酢酸エチル=19:1)により精製して、4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8-テトラメチルナフタレン-2-イル)アミノ]安息香酸エチルエステル(VI-2)を1.0 g(48%)得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.91 (2H, d, $J=8.8$ Hz), 7.27 (1H, d, $J=8.4$ Hz),

7.10 (1H, d, J=2.6 Hz), 6.96 (1H, dd, J=2.6, 8.8 Hz), 6.94 (2H, d, J=9.2 Hz), 4.33 (2H, q, J=7.0 Hz), 1.69 (4H, s), 1.37 (3H, t, J=7.3 Hz), 1.28 (6H, s), 1.27 (6H, s).

化合物VI-2 (118 mg) をエタノール (4 ml) に溶かし、20% KOH 水溶液 (0.5 ml) を加えて還流した。原料消失後、反応液を1 N 塩酸 30 ml にあけ塩化メチレンで抽出した。有機層を無水硫酸ナトリウムで脱水、濃縮して白色結晶 109 mg (定量的) として DA010を得た。

pale colored prisms (酢酸エチル-n-ヘキサン); mp 277 °C

¹H-NMR (400 MHz, CDCl₃ + DMSO-d₆) 7.89 (2H, dt, J=1.0, 8.8 Hz), 7.25 (1H, d, J=8.4 Hz), 7.10 (1H, d, J=2.2 Hz), 6.98 (1H, dd, J=2.6, 8.4 Hz), 6.97 (2H, dt, J=1.8, 8.8 Hz), 6.78 (1H, br s), 1.69 (4H, s), 1.28 (6H, s), 1.27 (6H, s)

Anal. Calcd for C₂₁H₂₅NO₂, C: 77.98%, H: 7.79%, N: 4.33%; Found C: 78.02%, H: 8.01%, N: 4.29%.

例18: 4-[N-メチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) アミノ] 安息香酸(DA011) の製造 (スキーム6)

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) アミノ] 安息香酸エチルエステル (VI-2) 242 mgを DMF 2 ml に溶かし、DMF (2 ml) に懸濁させたNaH (145 mg)を加えた。その後ヨウ化メチル (1.5 ml) を加え、室温で攪拌した。TLC で原料消失を確認した後、反応液を水 (50 ml) にあけ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン: 酢酸エチル=10:1) にて精製し、4-[N-メチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) アミノ] 安息香酸エチルエステル 269 mg (定量的) を得た。

Colorless needles (n-ヘキサン); mp 131 °C

¹H-NMR (400 MHz, CDCl₃) 7.86 (2H, dd, J=2.2, 9.16 Hz), 7.31 (1H, d, J=8.4 Hz), 7.13 (1H, d, J=2.6 Hz), 6.95 (1H, dd, J=2.2, 8.4 Hz), 6.74 (2H, dd,

J=2.2, 9.2 Hz), 4.32 (2H, q, J=7.0 Hz), 3.34 (3H, s), 1.70 (4H, s), 1.36 (3H, t, J=7.3 Hz), 1.30 (6H, s), 1.25 (6H, s)

Anal. Calcd for $C_{24}H_{31}NO_2$, C: 78.86%, H: 8.55%, N: 3.83%; Found C: 78.88%, H: 8.68%, N: 3.78%

上記エステル体 367 mg をエタノール 5 ml に溶かし、20% KOH 水溶液 1 ml を加えて環流した。原料消失後、反応液を1 N 塩酸 50 mlにあげ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮して白色結晶 334.5 mg(定量的)として DA011を得た。

colorless powders (n-ヘキサン); mp 252 °C

1H -NMR (400 MHz, $CDCl_3$) 7.92 (2H, dd, J=1.8, 9.2 Hz), 7.35 (1H, d, J=8.4 Hz), 7.17 (1H, d, J=2.2 Hz), 6.98 (1H, dd, J=2.6, 8.4 Hz), 6.76 (2H, dd, J=2.2, 9.2 Hz), 3.38 (3H, s), 1.73 (4H, s), 1.33 (6H, s), 1.28 (6H, s).

Anal. Calcd for $C_{22}H_{27}NO_2$, C: 78.30%, H: 8.07%, N: 4.15%; Found C: 78.16%, H: 8.14%, N: 4.16%.

例19: 4-[N-エチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA012) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) 249 mgをDMF (5 ml)に溶かし、DMF (5 ml) に懸濁させたNaH (134 mg)を加えた。その後ヨウ化エチル (3 ml)を加え、室温で攪拌した。TLC で原料消失を確認した後、反応液を水 (50 ml)にあげ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン: 酢酸エチル=10:1)にて精製し、4-[N- エチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル 269 mg (定量的)を得た。

Colorless needles (n-ヘキサン); mp 88.5°C

1H -NMR (400 MHz, $CDCl_3$) 7.83 (2H, dd, J=1.8, 9.2 Hz), 7.32 (1H, d, J=8.4 Hz), 7.10 (1H, d, J=2.2 Hz), 6.93 (1H, dd, J=2.2, 8.1 Hz), 6.65 (2H, dd,

J=2.2, 9.2 Hz), 4.31 (2H, q, J=7.3 Hz), 3.76 (2H, q, J=7.0 Hz), 1.70 (4H, s), 1.35 (3H, t, J=7.0 Hz), 1.30 (6H, s), 1.24 (6H, s), 1.24 (3H, t, J=7.3 Hz)

Anal. Calcd for $C_{25}H_{33}NO_2$, C: 79.11%, H: 8.76%, N: 3.69%; Found C: 78.84%, H: 8.86%, N: 3.40%

上記エステル体 (270 mg) をエタノール (8 ml) に溶かし、20% KOH 水溶液 2 ml を加えて還流した。原料消失後、反応液を1 N 塩酸 (40 ml) にあけ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮して白色結晶 251 mg (定量的) としてDA012 を得た。

colorless powders (n-ヘキサン- 塩化メチレン); mp 256 °C

1H -NMR (400 MHz, $CDCl_3$) 7.88 (2H, d, J=9.2 Hz), 7.33 (1H, d, J=8.4 Hz), 7.11 (1H, s), 6.93 (1H, d, J=8.4 Hz), 6.65 (2H, d, J=9.2 Hz), 3.77 (2H, q, J=7.3 Hz), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 1.25 (3H, t, J=7.0 Hz)

Anal. Calcd for $C_{23}H_{29}NO_2$, C: 78.59%, H: 8.32%, N: 3.99%; Found C: 78.81%, H: 8.23%, N: 4.09%.

例20: 4-[N-n-プロピル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA013) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) 252 mgをDMF (5 ml) に溶かし、DMF (5 ml) に懸濁させた NaH (135 mg) を加えた。その後ヨウ化n-プロピル (3 ml) を加え、室温で攪拌した。TLC で原料消失を確認した後、反応液を水 (30 ml) にあけ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン: 酢酸エチル=20:1) にて精製し、白色結晶 282 mg (99.6%) を得た。

Colorless powder (n-ヘキサン); mp 114 °C

1H -NMR (400 MHz, $CDCl_3$) 7.83 (2H, dd, J=1.8, 8.8 Hz), 7.32 (1H, d, J=8.4

Hz), 7.10 (1H, d, $J=2.2$ Hz), 6.93 (1H, dd, $J=2.6$ Hz, 8.4 Hz), 6.64 (2H, dd, $J=2.2$, 9.2 Hz), 4.31 (2H, q, $J=7.0$ Hz), 3.63 (2H, t, $J=7.7$ Hz), 1.71 (2H, hex, $J=7.3$ Hz), 1.70 (4H, s), 1.35 (3H, t, $J=7.3$ Hz), 1.31 (6H, s), 1.25 (6H, s), 0.94 (3H, t, $J=7.3$ Hz)

Anal. Calcd for $C_{26}H_{35}NO_2$, C: 79.34%, H: 8.96%, N: 3.56%; Found C: 79.21%, H: 8.75%, N: 3.48%.

上記エステル体 (282 mg) をエタノール (8 ml) に溶かし、20% KOH 水溶液 (2 ml) を加えて還流した。原料消失後、反応液を 1 N塩酸 (50 ml) にあけ、塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮して白色結晶 262 mg (定量的) としてDA013 を得た。

Colorless powder (n-ヘキサン); mp 235.5 °C

1H -NMR (400 MHz, $CDCl_3$) 7.87 (2H, d, $J=9.2$ Hz), 7.33 (1H, d, $J=8.1$ Hz), 7.11 (1H, d, $J=2.2$ Hz), 6.93 (1H, dd, $J=2.6$ Hz, 8.4 Hz), 6.63 (2H, d, $J=9.2$ Hz), 3.63 (2H, t, $J=7.7$ Hz), 1.67-1.76 (2H, m), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 0.94 (3H, t, $J=7.7$ Hz)

Anal. Calcd for $C_{24}H_{31}NO_2$, C: 78.86%, H: 8.55%, N: 3.83%; Found C: 78.64%, H: 8.46%, N: 3.84%.

例21:4-[N-n-ブチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA014) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) とヨウ化n-ブチルを用いて、例20の方法に従ってDA014 を合成した。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 216 °C

1H -NMR (400 MHz, $CDCl_3$) 7.87 (2H, d, $J=8.8$ Hz), 7.32 (1H, d, $J=8.4$ Hz), 7.10 (1H, s), 6.93 (1H, d, $J=6.6$ Hz), 6.63 (2H, d, $J=9.2$ Hz), 3.67 (2H, t, $J=7.7$ Hz), 1.70 (4H, s), 1.64-1.74 (2H, m), 1.37 (2H, hex, $J=7.7$ Hz), 1.31 (6H, s), 1.25 (6H, s), 0.94 (3H, t, $J=7.3$ Hz)

Anal. Calcd for $C_{25}H_{33}NO_2$, C: 79.11%, H: 8.76%, N: 3.69%; Found C: 79.23%, H: 8.68%, N: 3.71%.

例22: 4-[N-n-ペンチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸(DA015)の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸エチルエステル(VI-2)とヨウ化n-ペンチルを用いて、例20の方法に従ってDA015を合成した。

Colorless powder (n-ヘキサン-塩化メチレン); mp 219-221 °C

1H -NMR (400 MHz, $CDCl_3$) 7.88 (2H, dd, J=1.8, 8.8 Hz), 7.32 (1H, d, J=8.4 Hz), 7.11 (1H, d, J=2.6 Hz), 6.93 (1H, dd, J=2.6, 8.4 Hz), 6.63 (2H, dd, J=1.83, 9.2 Hz), 3.66 (2H, t, J=7.7 Hz), 1.70 (4H, s), 1.66-1.70 (2H, m), 1.31 (6H, s), 1.25 (6H, s), 1.22-1.37 (4H, m), 0.89 (3H, t, J=7.0 Hz)

Anal. Calcd for $C_{26}H_{35}NO_2$, C: 79.34%, H: 8.97%, N: 3.56%; Found C: 79.05%, H: 8.95%, N: 3.44%.

例23: 4-[N-n-ヘキシル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸(DA016)の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸エチルエステル(VI-2)とヨウ化n-ヘキシルを用いて、例20の方法に従ってDA016を合成した。

Colorless powder (n-ヘキサン-塩化メチレン); mp 199-200.5 °C

1H -NMR (400 MHz, $CDCl_3$) 7.87 (2H, dd, J=2.2, 9.2 Hz), 7.32 (1H, d, J=8.1 Hz), 7.10 (1H, d, J=2.6 Hz), 6.93 (1H, dd, J=2.6, 8.4 Hz), 6.63 (2H, dd, J=1.8, 8.8 Hz), 3.67 (2H, t, J=7.7 Hz), 1.70 (4H, s), 1.65-1.70 (2H, m), 1.31 (6H, s), 1.25 (6H, s), 1.29-1.46 (6H, m), 0.88 (3H, t, J=7.0 Hz).

Anal. Calcd for $C_{27}H_{37}NO_2$, C: 79.56%, H: 9.15%, N: 3.44%; Found C: 79.53%, H: 8.94%, N: 3.14%.

例24: 4-[N-n-ヘプチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸(DA017)の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸エチルエステル(VI-2)とヨウ化n-ヘプチルを用いて、例20の方法に従ってDA017を合成した。

Colorless powder (n-ヘキサン-塩化メチレン); mp 168 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.86 (2H, d, $J=9.2$ Hz), 7.32 (1H, d, $J=8.4$ Hz), 7.10 (1H, d, $J=1.8$ Hz), 6.93 (1H, dd, $J=2.2, 8.4$ Hz), 6.63 (2H, d, $J=8.8$ Hz), 3.66 (2H, t, $J=7.7$ Hz), 1.70 (4H, s), 1.70 (2H, br m), 1.31 (6H, s), 1.25-1.31 (8H, br m), 1.25 (6H, s), 0.87 (3H, t, $J=6.6$ Hz)

Anal. Calcd for $\text{C}_{28}\text{H}_{39}\text{NO}_2$, C: 79.76%, H: 9.32%, N: 3.32%; Found C: 79.80%, H: 9.62%, N: 3.06%.

例25: 4-[N-n-オクチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸(DA018)の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸エチルエステル(VI-2)とヨウ化n-オクチルを用いて、例20の方法に従ってDA018を合成した。

Colorless cotton (n-ヘキサン-塩化メチレン); mp 160 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.87 (2H, dd, $J=2.2, 9.2$ Hz), 7.32 (1H, d, $J=8.4$ Hz), 7.10 (1H, d, $J=2.2$ Hz), 6.92 (1H, dd, $J=2.2, 8.4$ Hz), 6.63 (2H, d, $J=9.2$ Hz), 3.66 (2H, t, $J=8.1$ Hz), 1.70 (4H, s), 1.70 (2H, m), 1.31 (6H, s), 1.26 (10H, m), 1.25 (6H, s), 0.87 (3H, t, $J=6.6$ Hz)

Anal. Calcd for $\text{C}_{29}\text{H}_{41}\text{NO}_2$, C: 79.95%, H: 9.49%, N: 3.22%; Found C: 79.92%, H: 9.54%, N: 3.18%.

例26 : 4-[N-(プロピン-3-イル)-N-(5, 6, 7, 8- テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA020) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化アセチレニルメチルを用いて、例20の方法に従って DA020を合成した。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 269-270 °C (dec.)

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.93 (2H, dd, $J=2.2, 9.2$ Hz), 7.34 (1H, d, $J=8.4$ Hz), 7.21 (1H, d, $J=2.2$ Hz), 7.03 (1H, dd, $J=2.2, 8.4$ Hz), 6.80 (2H, dd, $J=2.2, 9.2$ Hz), 4.41 (2H, d, $J=2.6$ Hz), 2.29 (1H, t, $J=2.2$ Hz), 1.71 (4H, s), 1.31 (6H, s), 1.25 (6H, s)

例27 : 4-[N-(プロペン-3-イル)-N-(5, 6, 7, 8- テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA021) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化アリルを用いて、例20の方法に従ってDA021 を合成した。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 247-248 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.87 (2H, dd, $J=1.8, 9.2$ Hz), 7.32 (1H, d, $J=8.1$ Hz), 7.16 (1H, d, $J=2.2$ Hz), 6.98 (1H, dd, $J=2.2, 8.1$ Hz), 6.71 (2H, dd, $J=1.8, 9.2$ Hz), 5.94 (1H, ddt, $J=5.2, 10.3, 17.2$ Hz), 5.28 (1H, dd, $J=1.5, 17.2$ Hz), 5.22 (1H, dd, $J=1.5, 10.3$ Hz), 4.35 (1H, dd, $J=1.8, 4.8$ Hz), 1.70 (4H, s), 1.30 (6H, s), 1.24 (6H, s)

Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_2$, C: 79.30%, H: 8.04%, N: 3.85%; Found C: 79.08%, H: 8.18%, N: 4.15%.

例28： 4-[N-イソプロピル-N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA022) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) 113 mg、および炭酸カリウム (89 mg)をヨウ化イソプロピルに溶かし、48時間環流した。反応液を水 (30 ml)にあげ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水し、溶媒留去後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン：酢酸エチル=20：1)により精製して、13 mg (10 %)を得た。

Colorless prisms (n-ヘキサン); mp 81°C

^1H -NMR (400 MHz, CDCl_3) 7.80 (2H, dd, $J=2.2, 9.2$ Hz), 7.33 (1H, d, $J=8.4$ Hz), 6.99 (1H, d, $J=2.2$ Hz), 6.82 (1H, dd, $J=2.2, 8.4$ Hz), 6.50 (2H, dd, $J=2.6, 9.2$ Hz), 4.35 (1H, hep, $J=6.6$ Hz), 4.29 (2H, q, $J = 7.0$ Hz), 1.71 (4H, s), 1.33 (3H, t, $J=7.0$ Hz), 1.31 (6H, s), 1.24 (6H, s), 1.14 (6H, d, $J=6.6$ Hz).

上記エステル体 (45 mg)をエタノール (4 ml) に溶かし、20% KOH 水溶液 (1 ml) を加えて還流した。原料消失後、反応液を1 N 塩酸 (30 ml)にあげ、塩化メチレンで抽出した。有機層を無水硫酸ナトリウムで脱水し、溶媒留去して40 mg (98 %) のDA022 を得た。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 259 °C

^1H -NMR (400 MHz, CDCl_3) 7.85 (2H, dd, $J=2.2, 9.2$ Hz), 7.34 (1H, d, $J=8.4$ Hz), 6.99 (1H, d, $J=2.2$ Hz), 6.82 (1H, dd, $J=2.2, 8.1$ Hz), 6.51 (2H, d, $J=9.2$ Hz), 4.37 (1H, hep, $J=6.6$ Hz), 1.71 (4H, s), 1.32 (6H, s), 1.24 (6H, s), 1.15 (6H, d, $J=6.6$ Hz)

例29： 4-[N-シクロプロピル-N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA023) の製造

シクロプロピルアミン (1 ml) と4-ヨード安息香酸エチル (407 mg) 及びtert-BuONa (180 mg) を無水トルエン (10 ml)に溶かし、アルゴン置換下、トリス(

ジベンジリデンアセトン) ジパラジウム(0) (54 mg)、(R)-BINAP (102 mg)を加え、80°Cで加熱した。4 時間後、室温まで冷まし、水 30 mlにあげエーテルで抽出した。有機層を無水硫酸ナトリウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル =20 : 1) により精製して、4-(シクロプロピルアミノ) 安息香酸エチルエステルを 150 mg (56%) 得た。

Colorless needles (n-ヘキサン); mp 69 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.88 (2H, dd, $J=2.2, 8.8$ Hz), 6.74 (2H, dd, $J=2.2, 8.8$ Hz), 4.53 (1H, brs), 4.32 (2H, q, $J=7.0$ Hz), 2.48 (1H, dtt, $J=1.5, 2.6, 6.2$ Hz), 1.36 (3H, t, $J=7.0$ Hz), 0.79 (2H, ddd, $J=4.4, 6.6, 7.0$ Hz), 0.54 (2H, ddd, $J=3.7, 4.8, 6.6$ Hz)

Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$, C: 70.22%, H: 7.37%, N: 6.83%; Found C: 70.20%, H: 7.23%, N: 6.68%.

4-(シクロプロピルアミノ) 安息香酸エチルエステル (97 mg)、6-ブromo-1,2,3,4-テトラヒドロ-1,1,4,4-テトラメチルナフタレン (121.5 mg) 及びtert-BuONa (67 mg)を無水トルエン (5 ml) に溶かし、アルゴン置換下、トリス(ジベンジリデンアセトン) ジパラジウム(0) (24 mg)、(R)-BINAP (40.5 mg) を加え、80°Cで加熱した。1.5 時間後、室温まで冷却し、水 30 mlにあげ塩化メチレンで抽出した。有機層を飽和食塩水で洗い、無水硫酸ナトリウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル= 20 : 1) により精製し、4-[N-シクロプロピル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) アミノ] 安息香酸エチルエステル 42 mg (20 %) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.86 (2H, dd, $J=2.2, 9.2$ Hz), 7.29 (1H, d, $J=8.1$ Hz), 7.02 (1H, d, $J=2.6$ Hz), 6.93 (2H, dd, $J=1.8, 8.8$ Hz), 6.87 (dd, $J=2.2, 8.1$ Hz), 4.31 (2H, q, $J=7.3$ Hz), 2.80 (1H, tt, $J=3.7, 6.6$ Hz), 1.70 (4H, s), 1.35 (3H, t, $J=7.3$ Hz), 1.30 (6H, s), 1.24 (6H, s), 0.89 (2H, ddd, $J=4.8, 6.2, 7.0$ Hz), 0.63 (2H, ddd, $J=3.7, 5.1, 7.0$ Hz).

上記エステル体 (42 mg)をエタノール (2 ml) に溶かし、20% KOH 水溶液 (0.

5 ml) を加えて還流した。2 時間後、反応液を 1N NaOH 水溶液 (30 ml) にあけエーテルで洗い、水層を濃塩酸で強酸性とし、塩化メチレンで抽出した。有機層を無水硫酸ナトリウムで脱水、濃縮して黄白色結晶 14 mg (35%) を得た。得られた結晶を活性炭処理をしたのち、再結晶により白色結晶として DA023 を得た。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 260-261 °C(dec.)

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.89 (2H, dd, $J=2.2, 9.2$ Hz), 7.30 (1H, d, $J=8.43$ Hz), 7.02 (1H, d, $J=2.2$ Hz), 6.94 (1H, dd, $J=2.2, 9.2$ Hz), 6.87 (2H, dd, $J=2.2, 8.4$ Hz), 2.82 (1H, tt, $J=4.0, 7.0$ Hz), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 0.90 (2H, ddd, $J=5.1, 6.6, 7.0$ Hz), 0.64 (2H, ddd, $J=5.1, 5.5, 7.3$ Hz)

例30: 4-[N-シクロプロピルメチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA024) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化シクロプロピルメチルを用いて、例 20の方法に従ってDA024 を合成した。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 245 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.88 (2H, dd, $J=1.8, 9.2$ Hz), 7.32 (1H, d, $J=8.4$ Hz), 7.16 (1H, d, $J=2.6$ Hz), 6.95 (1H, dd, $J=2.2, 8.1$ Hz), 6.68 (2H, dd, $J=1.8, 9.2$ Hz), 3.56 (2H, d, $J=6.6$ Hz), 1.70 (4H, s), 1.31 (6H, s), 1.25 (6H, s), 1.15-1.22 (1H, m), 0.50 (2H, ddd, $J=4.4, 5.9, 8.1$ Hz), 0.14 (2H, q, $J=4.8$ Hz)

Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{NO}_2$, C: 79.53%, H: 8.28%, N: 3.71%; Found C: 79.33%, H: 8.36%, N: 3.82%.

例31： 4-[N-イソブチル-N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA025) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) とヨウ化イソブチルを用いて、例20の方法に従ってDA025 を合成した。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 232 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.85 (2H, dd, $J=1.8, 9.2$ Hz), 7.31 (1H, d, $J=8.4$ Hz), 7.12 (1H, d, $J=2.6$ Hz), 6.93 (1H, dd, $J=2.2, 8.4$ Hz), 6.67 (2H, d, $J=9.2$ Hz), 3.52 (2H, d, $J=7.3$ Hz), 2.08 (1H, 7th, $J=7.0$ Hz), 1.70 (4H, s), 1.30 (6H, s), 1.24 (6H, s), 0.96 (6H, d, $J=6.6$ Hz)

Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_2$, C: 79.11%, H: 8.76%, N: 3.69%; Found C: 79.10%, H: 8.81%, N: 3.65%.

例32： 4-[N-イソペンテニル-N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA028) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化プレニルを用いて、例20の方法に従ってDA028 を合成した。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 215 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.87 (2H, dd, $J=2.2, 9.2$ Hz), 7.30 (1H, d, $J=8.4$ Hz), 7.11 (1H, d, $J=2.2$ Hz), 6.94 (1H, dd, $J=2.2, 8.4$ Hz), 6.67 (2H, dd, $J=2.2, 9.2$ Hz), 5.33 (1H, t, $J=5.86$ Hz), 4.29 (2H, d, $J=5.49$ Hz), 1.72 (3H, s), 1.70 (4H, s), 1.61 (3H, s), 1.30 (6H, s), 1.24 (6H, s)

例33： 4-[N-シクロブチルメチル-N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA030) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化シクロブチルメチルを用いて、例20

の方法に従ってDA030 を合成した。

Colorless needles (n- ヘキサン- 塩化メチレン); mp 232 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.85 (2H, dd, $J=2.2, 9.2$ Hz), 7.31 (1H, d, $J=8.4$ Hz), 7.07 (1H, d, $J=2.2$ Hz), 6.89 (1H, dd, $J=2.2, 8.4$ Hz), 6.60 (2H, dd, $J=1.8, 8.8$ Hz), 3.70 (2H, d, $J=7.0$ Hz), 2.74 (1H, 5th, $J=7.7$ Hz), 2.01 (2H, m), 1.82 (2H, m), 1.70 (4H, s), 1.66 (2H, m), 1.30 (6H, s), 1.24 (6H, s)

Anal. Calcd for $\text{C}_{26}\text{H}_{33}\text{NO}_2$, C: 79.75%, H: 8.50%, N: 3.58%; Found C: 79.82%, H: 8.53%, N: 3.61%.

例34: 4-[N-シクロヘキシルメチル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA036) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化シクロヘキシルメチルを用いて、例20の方法に従ってDA036 を合成した。

Colorless cubes (n- ヘキサン- 塩化メチレン); mp 230-231 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.86 (2H, d, $J=9.2$ Hz), 7.31 (1H, d, $J=8.4$ Hz), 7.10 (1H, d, $J=2.2$ Hz), 6.92 (1H, dd, $J=2.2, 8.4$ Hz), 6.65 (2H, dd, $J=9.2$ Hz), 3.59 (2H, d, $J=7.0$ Hz), 1.75 (6H, m), 1.70 (4H, s), 1.31 (6H, s), 1.24 (6H, s), 1.16 (3H, m), 0.95 (2H, m)

Anal. Calcd for $\text{C}_{28}\text{H}_{37}\text{NO}_2$, C: 80.15%, H: 8.89%, N: 3.34%; Found C: 79.86%, H: 8.89%, N: 3.33%.

例35: 4-[N-ベンジル-N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA040) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化ベンジルを用いて、例20の方法に従ってDA040 を合成した。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 272-273 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.84 (2H, dd, $J=2.2, 9.2$ Hz), 7.32 (4H, d, $J=4.8$ Hz), 7.30 (1H, d, $J=7.3$ Hz), 7.23-7.25 (1H, m), 7.21 (1H, d, $J=2.2$ Hz), 7.04 (1H, dd, $J=2.2, 8.4$ Hz), 6.73 (2H, dd, $J=1.8, 9.2$ Hz), 5.00 (2H, s), 1.69 (4H, s), 1.29 (6H, s), 1.22 (6H, s)

Anal. Calcd for $\text{C}_{28}\text{H}_{31}\text{NO}_2$, C: 81.32%, H: 7.56%, N: 3.39%; Found C: 81.05%, H: 7.49%, N: 3.57%.

例36: 4-[N-(4-メチルベンジル)-N-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA041) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化 (4-メチルベンジル) を用いて、例20の方法に従ってDA041 を合成した。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 246-248 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.83 (2H, dd, $J=2.2, 9.2$ Hz), 7.30 (1H, d, $J=8.4$ Hz), 7.21 (1H, d, $J=2.2$ Hz), 7.20 (2H, d, $J=6.6$ Hz), 7.12 (2H, d, $J=8.1$ Hz), 7.03 (1H, dd, $J=2.2, 8.4$ Hz), 6.73 (2H, dd, $J=2.9, 9.2$ Hz), 4.96 (2H, s), 2.32 (3H, s), 1.68 (4H, s), 1.29 (6H, s), 1.22 (6H, s)

Anal. Calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_2$, C: 81.46%, H: 7.78%, N: 3.28%; Found C: 81.28%, H: 7.82%, N: 3.44%.

例37: 4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル)-N-(4- トリフルオロメチルベンジル) アミノ] 安息香酸(DA042) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化 (4-トリフルオロメチルベンジル) を用いて、例20の方法に従ってDA042 を合成した。

Colorless powder (n-ヘキサン); mp 209-210 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.86 (2H, dd, $J=2.2, 9.2$ Hz), 7.58 (2H, d, $J=8.1$

Hz), 7.44 (2H, d, J=8.4 Hz), 7.32 (1H, d, J=8.4 Hz), 7.19 (1H, d, J=2.2 Hz), 7.02 (1H, dd, J=2.2, 8.4 Hz), 6.70 (2H, d, J=8.8 Hz), 5.04 (2H, s), 1.69 (4H, s), 1.29 (6H, s), 1.22 (6H, s)

Anal. Calcd for $C_{29}H_{30}NO_2F_3$, C: 72.33%, H: 6.28%, N: 2.91%; Found C: 72.15%, H: 6.41%, N: 2.94%.

例38 : 4-[N-(4-エトキシ-2,3,5,6- テトラフルオロベンジル)-N-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA045) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化 (ペンタフルオロベンジル) を用いて、例20の方法に従ってDA045 を合成した。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 227-229 °C

1H -NMR (400 MHz, $CDCl_3$) 7.90 (2H, dd, J=1.8, 8.8 Hz), 7.26 (1H, d, J=8.4 Hz), 6.98 (1H, d, J=2.2 Hz), 6.87 (1H, dd, J=2.2, 8.4 Hz), 6.75 (2H, dd, J=1.8, 8.8 Hz), 4.92 (2H, s), 4.22 (q, J=7.0 Hz), 1.66 (4H, s), 1.36 (3H, t, J=7.0 Hz), 1.25 (6H, s), 1.16 (6H, s)

Anal. Calcd for $C_{30}H_{31}F_4NO_3$, C: 68.04%, H: 5.90%, N: 2.65%; Found C: 67.78%, H: 5.89%, N: 2.61%.

例39 : 4-[N-(2-ビフェニルメチル)-N-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA046) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化ビフェニルメチルを用いて、例20の方法に従ってDA046 を合成した。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 237-239 °C

1H -NMR (400 MHz, $CDCl_3$) 7.80(2H, d, J=8.8 Hz), 7.79-7.48 (1H, m), 7.35-7.44 (4H, m), 7.23-7.31 (6H, m), 7.15 (1H, d, J=2.6 Hz), 6.98 (1H, dd, J=2.

2, 8.8 Hz), 6.64 (2H, d, J=9.2 Hz), 4.87 (2H, s), 1.68 (4H, s), 1.28 (6H, s), 1.19 (6H, s)

Anal. Calcd for $C_{34}H_{35}NO_2$, C: 83.40%, H: 7.21%, N: 2.86%; Found C: 83.11%, H: 7.50%, N: 2.75%.

例40: 4-[N-(2-ナフチルメチル)-N-(5, 6, 7, 8- テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA048) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) と臭化-2- ナフチルメチルを用いて、例20の方法に従ってDA048 を合成した。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 233 °C

1H -NMR (400 MHz, $CDCl_3$) 7.84 (2H, dd, J=2.2, 9.2 Hz), 7.78 (4H, m), 7.44 (3H, m), 7.31 (1H, d, J=8.4 Hz), 7.27 (1H, d, J=2.6 Hz), 7.09 (1H, dd, J=2.2, 8.4 Hz), 6.79 (2H, dd, J=2.2, 9.2 Hz), 5.15 (2H, s), 1.68 (4H, s), 1.28 (6H, s), 1.22 (6H, s)

Anal. Calcd for $C_{32}H_{33}NO_2$, C: 82.90%, H: 7.18%, N: 3.02%; Found C: 82.66%, H: 7.48%, N: 2.73%.

例41: 4-[N-アセチル-N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA051) の製造

4-[N-(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) 605 mgを無水トルエン (15 ml)に溶かし、塩化アセチル (1 ml) を加えてアルゴン下で一晩還流した。溶媒を減圧留去し、残渣をフラッシュシリカゲルカラムクロマトグラフィー(n-ヘキサン: 酢酸エチル= 10:1)により精製して、白色粗結晶を677 mg (定量的) 得た。

Colorless cubes (n-ヘキサン); mp 102 °C

1H -NMR (400 MHz, $CDCl_3$) 8.00 (2H, d, J=8.4 Hz), 7.33 (2H, dd, J=1.8, 8.8 Hz), 7.31 (1H, d, J= 8.8 Hz), 7.15 (1H, d, J=2.6 Hz), 6.95 (1H, dd, J=2.

2, 8.4 Hz), 4.36 (2H, q, J=7.0 Hz), 2.05 (3H, s), 1.69 (4H, s), 1.37 (3H, t, J=7.0 Hz), 1.28 (6H, s), 1.24 (6H, s)

Anal. Calcd for $C_{25}H_{31}NO_3$, C: 76.30%, H: 7.94%, N: 3.56%; Found C: 76.26%, H: 7.93%, N: 3.51%.

上記エステル体 (404 mg) をエタノール (10 ml) に溶かし、5% NaOH 水溶液 (0.9 ml) を加えて室温で一晩攪拌した。溶媒を減圧留去し、残渣に水 (0.5 ml) および濃塩酸 (5 ml) を加え、析出した結晶を濾取して乾燥し、白色結晶 342 mg (91%) として DA051 を得た。

Colorless powder (n-ヘキサン); mp 222 °C

1H -NMR (400 MHz, $CDCl_3$) 8.04 (2H, d, J=8.4 Hz), 7.36 (2H, dd, J=2.2, 8.8 Hz), 7.33 (1H, d, J=8.1 Hz), 7.16 (1H, d, J=2.2 Hz), 6.96 (1H, dd, J=2.6, 8.4 Hz), 2.06 (3H, s), 1.70 (4H, s), 1.29 (6H, s), 1.25 (6H, s)

Anal. Calcd for $C_{23}H_{27}NO_3$, C: 75.59%, H: 7.45%, N: 3.83%; Found C: 75.29%, H: 7.54%, N: 3.65%.

例42: 4-[N-ベンゾイル-N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) アミノ] 安息香酸 (DA055) の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル) アミノ] 安息香酸エチルエステル (VI-2) 104 mg を無水ベンゼン (5 ml) に溶かし、ベンゾイルクロライド (1 ml) およびピリジン (1 ml) を加えて攪拌した。原料消失後、反応液を飽和重曹水にあげ、塩化メチレンで抽出した。有機層を 1 N 塩酸 (30 ml) で洗い、無水硫酸ナトリウムで脱水して、溶媒を減圧留去した。残渣をフラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン: 酢酸エチル=20:1) により精製して、白色粗結晶 130 mg (96.5%) を得た。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 149 °C

1H -NMR (400 MHz, $CDCl_3$) 7.97 (2H, d, J=8.4 Hz), 7.41 (2H, d, J=8.4 Hz), 7.18-7.30 (6H, m), 6.91 (1H, d, J=2.2 Hz), 6.84 (1H, dd, J=2.6, 8.4 Hz), 4.36 (2H, q, J=7.0 Hz), 1.61 (4H, s), 1.38 (3H, t, J=6.96 Hz), 1.23 (6H,

s), 1.02 (6H, s)

Anal. Calcd for $C_{30}H_{33}NO_3$, C: 79.09%, H: 7.30%, N: 3.08%; Found C: 78.94%, H: 7.29%, N: 3.08%.

上記エステル体 (79 mg) をエタノール (4 ml) に溶かし、5% NaOH 水溶液 (1 ml) を加えて室温で5時間攪拌した。反応液を1 N 塩酸にあげ塩化メチレンで抽出した。有機層を無水硫酸ナトリウムで脱水し、溶媒留去してDA055 を 77 mg (定量的) 得た。

Colorless cotton (n-ヘキサン- 塩化メチレン); mp 228-229.5 °C

1H -NMR (400 MHz, $CDCl_3$) 8.03 (2H, dd, J=1.8, 8.8 Hz), 7.42 (2H, dd, J=1.5 Hz, 8.4 Hz), 7.19-7.30 (6H, m), 6.91 (1H, d, J=2.6 Hz), 6.85 (1H, dd, J=2.6 Hz, 8.4 Hz), 1.61 (4H, s), 1.23 (6H, s), 1.02 (6H, s)

Anal. Calcd for $C_{28}H_{29}NO_3$, C: 78.66%, H: 6.84%, N: 3.28%; Found C: 78.77%, H: 6.95%, N: 3.19%.

例43: 4-[N-(4-カルボキシベンゾイル)-N-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸(DA058) の製造

4-[N-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチルナフタレン-2- イル) アミノ] 安息香酸エチルエステル (VI-2) 153.0 mgを無水ベンゼン (5 ml) に溶かし、テレフタル酸モノメチルエステルクロライド (210 mg) およびピリジン 2 滴を加えて攪拌した。原料消失後、反応液を飽和重曹水にあげ、塩化メチレンで抽出した。有機層を1 N 塩酸 (30 ml) で洗い、無水硫酸ナトリウムで脱水して溶媒を減圧留去し、残査をフラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン: 酢酸エチル=10:1) により精製して、白色粗結晶を 191 mg(定量的) 得た。

Colorless powder (n-ヘキサン); mp 135 °C

1H -NMR (400 MHz, $CDCl_3$) 7.98 (2H, d, J=8.4 Hz), 7.88 (2H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.21 (1H, d, J=8.4 Hz), 6.92 (1H, s), 6.84 (1H, dd, J=2.2, 8.4 Hz), 4.36 (2H, q, J=7.3 Hz), 3.89 (3H, s), 1.61 (4H, s), 1.38 (3H, t, J=7.0 Hz), 1.23 (6H, s), 1.03 (6H,

s)

Anal. Calcd for $C_{32}H_{35}NO_5$, C: 74.83%, H: 6.87%, N: 2.73%; Found C: 74.75%, H: 7.00%, N: 2.44%.

上記エステル体 (86.3 mg) をエタノール (50 ml) に溶かし、5% NaOH 水溶液 (2 ml) を加え室温で4時間攪拌した。反応液を1 N 塩酸にあげ塩化メチレンおよび酢酸エチルで抽出した。有機層を硫酸マグネシウムで脱水し、溶媒留去して白色結晶 78.2 mg (98.8%) として DA058を得た。

Colorless powder (n-ヘキサン); mp >300 °C

1H -NMR (400 MHz, $CDCl_3$) 7.90 (2H, d, J=8.4 Hz), 7.78 (2H, d, J=8.4 Hz), 7.50 (2H, d, J=8.1 Hz), 7.43 (1H, s), 7.35 (2H, d, J=8.4 Hz), 7.29 (1H, d, J=8.4 Hz), 6.92 (1H, d, J=8.4 Hz), 1.56 (4H, s), 1.18 (6H, s), 1.02 (6H, s)

例44: 4-[N- エチル-N-(5,6,7,8-テトラヒドロ-3,5,5,8,8-ペンタメチルナフタレン-2-イル) アミノ] 安息香酸(DA112) の製造 (スキーム7)

1,2,3,4-テトラヒドロ-1,1,4,4,6-ペンタメチルナフタレン (VII-1, 21.888 g) を酢酸 (80 ml) に溶かし、氷冷下塩酸・硫酸混酸をゆっくり加え室温で攪拌した。3時間後、反応液を水 (200 ml) にあげ、析出した結晶を濾取し、水で洗った後に塩化メチレンに溶解した。この有機層を飽和重曹水、食塩水で順次洗い、硫酸マグネシウムで脱水し、溶媒留去した。得られた粗結晶をメタノールから再結晶して7-ニトロ-1,2,3,4-テトラヒドロ-1,1,4,4,6-ペンタメチルナフタレン (VII-2) 14.59 g (54.5%) を白色結晶として得た。

1H -NMR (400 MHz, $CDCl_3$) 7.96 (1H, s), 7.21 (1H, s), 2.56 (3H, s), 1.72 (4H, s), 1.30 (6H, s), 1.29 (6H, s).

上記ニトロ体 (VII-2) 14.59 g を酢酸エチル (200 ml) およびエタノール (100 ml) に溶かし、10% Pd/C (1.74 g) を加えて接触還元を行った。反応液をセライト濾過し、濾液を留去して得られた粗結晶をフラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン: 酢酸エチル = 25:1) により精製して、7-アミノ-1,2,

3, 4- テトラヒドロ-1, 1, 4, 4, 6- ペンタメチルナフタレン(VII-3) 12.14 g (94.6 %) を黄白色結晶として得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 6.98 (1H, s), 6.63 (1H, s), 3.61 (2H, br s), 2.14 (3H, s), 1.64 (4H, s), 1.24 (12H, s).

上記アミノ体 (VII-3) 1.085 g、4-ヨード安息香酸エチル (1.676 g) 及び *tert*-BuONa (616 mg) を無水トルエン (20 ml) に溶解し、アルゴン置換下でトリス (ジベンジリデンアセトン) ジパラジウム(0) (101.5 mg)、(R)-BINAP (163.8 mg) を加えて還流した。3 時間後、反応液を室温まで冷やし、水100 ml にあけてエーテルで抽出した。有機層を無水硫酸ナトリウムで脱水し、濃縮した後、残渣をフラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 10 : 1) により精製して、4-[N-(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8- ペンタメチルナフタレン-2-イル) アミノ] 安息香酸エチルエステル (VII-4) を 1.095 g (60%) 得た。

Colorless needles (n-ヘキサン); mp 173-175 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.89 (2H, dd, $J=1.83$ Hz, 8.8 Hz), 7.21 (1H, s), 7.16 (1H, s), 6.77 (2H, dd, $J=1.8$ Hz, 8.8 Hz), 4.33 (2H, q, $J=7.0$ Hz), 2.19 (3H, s), 1.68 (4H, s), 1.37 (3H, t, $J=7.0$ Hz), 1.29 (6H, s), 1.24 (6H, s)

Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_2$, C: 78.86%, H: 8.55%, N: 3.83%; Found C: 79.05%, H: 8.80%, N: 3.58%.

上記アミノ体 (VII-4, 92 mg) を DMF (2 ml) に溶かし、DMF (2 ml) に懸濁させた NaH (61.5 mg) を加えた。その後ヨウ化エチル (1 ml) を加え、室温で攪拌した。TLC で原料消失を確認した後、反応液を水 (30 ml) にあけ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 20 : 1) にて精製し、4-[N-エチル-N-(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8- ペンタメチルナフタレン-2-イル) アミノ] 安息香酸エチルエステル 98 mg (99%) を得た。

Colorless powder (n-ヘキサン); mp 94°C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.83 (2H, d, $J=8.8$ Hz), 7.20 (1H, s), 7.00 (1H,

s), 6.43 (2H, d, J=9.2 Hz), 4.30 (2H, q, J=7.3 Hz), 3.66 (2H, d, J=6.6 Hz), 2.03 (3H, s), 1.69 (4H, s), 1.34 (3H, t, J=7.0 Hz), 1.31 (6H, s), 1.25 (3H, t, J=7.3 Hz), 1.23 (6H, s)

Anal. Calcd for $C_{26}H_{35}NO_2$, C: 79.34%, H: 8.96%, N: 3.56%; Found C: 79.12%, H: 8.93%, N: 3.57%.

上記エステル体 (83 mg) をエタノール (4 ml) に溶かし、20% KOH 水溶液 1 ml を加えて環流した。原料消失後、反応液を1 N 塩酸 (40 ml) にあけ、塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水し、溶媒を留去してDA112 を77 mg(定量的) 得た。

Colorless powder (n-ヘキサン- 塩化メチレン); mp 266 °C

1H -NMR (400 MHz, $CDCl_3$) 7.87 (2H, d, J=9.2 Hz), 7.20 (1H, s), 7.00 (1H, s), 6.45 (2H, d, J=8.8 Hz), 3.67 (2H, br), 2.04 (1H, s), 1.69 (4H, s), 1.31 (6H, s), 1.26 (3H, t, J=7.0 Hz), 1.23 (6H, s)

Anal Calcd for $C_{24}H_{31}NO_2$, C: 78.86%, H: 8.55%, N: 3.83%; Found C: 78.56%, H: 8.71%, N: 3.82%.

例45: 4-[N-n-プロピル-N-(5,6,7,8-テトラヒドロ-3,5,5,8,8-ペンタメチルナフタレン-2-イル) アミノ] 安息香酸(DA113) の製造

化合物 VII-4とヨウ化n-プロピルを用いて、例44の方法に従ってDA113 を合成した。

Colorless powder (n-ヘキサン); mp 245 °C

1H -NMR (400 MHz, $CDCl_3$) 7.86 (2H, d, J=9.2 Hz), 7.20 (1H, s), 7.00 (1H, s), 6.42 (2H, d, J=8.8 Hz), 3.52 (2H, br s), 2.02 (3H, s), 1.72 (2H, hep, J=7.7 Hz), 1.69 (4H, s), 1.31 (6H, s), 1.23 (6H, s), 0.95 (3H, t, J=7.7 Hz)

Anal. Calcd for $C_{25}H_{33}NO_2$, C: 79.11%, H: 8.76%, N: 3.69%; Found C: 79.17%, H: 8.89%, N: 3.64%.

例46: 4-[N- イソプロピルメチル-N-(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8- ペンタメチルナフタレン-2- イル) アミノ] 安息香酸(DA122) の製造

化合物VII-4 (299 mg)及び炭酸カリウム (499 mg) をヨウ化イソプロピルに溶かし、封管中150 °Cで7日間加熱した。反応液を濾過し、濾液を無水硫酸ナトリウムで脱水して濃縮した。得られた残渣をフラッシュカラムクロマトグラフィー(n-ヘキサン: 酢酸エチル=20:1) で精製して無色透明油状物質 7 mg (2%)を得た。
 $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.82 (2H, d, $J=9.2$ Hz), 7.18 (1H, s), 6.91 (1H, s), 6.41 (2H, d, $J=8.8$ Hz), 4.34 (1H, hept, $J=7.0$ Hz), 4.29 (2H, q, $J=7.3$ Hz), 2.01 (3H, s), 1.69 (4H, s), 1.33 (3H, t, $J=7.3$ Hz), 1.30 (6H, s), 1.22 (6H, s), 1.15 (6H, s).

上記エステル体 (12 mg)をエタノール (3 ml) に溶かし、20% KOH 水溶液 0.5 ml を加えて環流した。原料消失後、反応液を1 N 塩酸 (20 ml)にあげ、塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水し、溶媒を留去してDA122を得た。

Colorless cubes(n-ヘキサン- 塩化メチレン); mp 257 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.85 (2H, d, $J=9.2$ Hz), 7.19 (1H, s), 6.91 (1H, s), 6.43 (2H, d, $J=9.2$ Hz), 4.36 (1H, pent, $J=7.0$ Hz), 2.01 (3H, s), 1.69 (4H, s), 1.31 (6H, s), 1.23 (6H, s), 1.16 (6H, brs).

例47: 4-[N- シクロプロピルメチル-N-(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8- ペンタメチルナフタレン-2- イル) アミノ] 安息香酸(DA124) の製造

化合物VII-4 と臭化シクロプロピルメチルを用いて、例44の方法に従ってDA124を合成した。

Colorless plates (n-ヘキサン- 塩化メチレン); mp 213 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.88 (2H, d, $J=9.2$ Hz), 7.17 (1H, s), 6.50 (2H, d, $J=8.8$ Hz), 3.50 (2H, brs), 2.03 (3H, s), 1.69 (4H, s), 1.30 (6H, s), 1.24 (6H, s), 1.22 (1H, m), 0.51 (2H, ddd, $J=4.8, 5.5, 8.1$ Hz), 0.13 (2H, q, $J=4.8$ Hz).

例48：4-[N- イソブチル-N-(5, 6, 7, 8-テトラヒドロ-3, 5, 5, 8, 8- ペンタメチルナフトレン-2- イル) アミノ] 安息香酸(DA125) の製造

化合物VII-4 とヨウ化イソブチルを用いて、例44の方法に従ってDA125 を合成した。

Colorless cotton (n-ヘキサン- 塩化メチレン); mp 245 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.85 (2H, d, $J=9.2$ Hz), 7.18 (1H, s), 7.07 (1H, s), 6.44 (2H, d, $J=9.2$ Hz), 3.40 (2H, brs), 1.67 (1H, hept, $J=7.0$ Hz), 1.98 (3H, s), 1.69 (4H, s), 1.31 (6H, s), 1.24 (6H, s), 0.99 (6H, d, $J=6.6$ Hz).

例49：4-[N-エチル-N-(3, 5-ジ-tert-ブチルフェニル) アミノ] 安息香酸(DA212) の製造 (スキーム 8)

3, 5- ジ-tert-ブチルアニリン (VIII-1) 1.087 g、4-ヨード安息香酸エチル(1817 g)及びtert-BuONa (667.5 mg) を無水トルエン (20 ml)に溶かし、アルゴン置換下でトリス (ジベンジリデンアセトン) ジパラジウム(0) 106 mg、(R)-BINAP (176 mg)を加えて還流した。2時間後、反応液を室温まで冷却し、水 (100 ml) にあけてエーテルで抽出した。有機層を無水硫酸ナトリウムで脱水し、濃縮した後、残渣をフラッシュシリカゲルカラムクロマトグラフィー(n-ヘキサン：酢酸エチル=20：1)により精製し、4-[N-(3, 5-ジ-tert-ブチルフェニル) アミノ] 安息香酸エチルエステル(VIII-2)を 1.28 g (68%) 得た。

Colorless needles (n-ヘキサン); mp 123 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.92 (2H, dd, $J=1.8, 8.8$ Hz), 7.14 (1H, t, $J=1.8$ Hz), 7.03 (2H, d, $J=1.5$ Hz), 6.96 (2H, dd, $J=1.8, 8.8$ Hz), 6.01 (1H, br s), 4.33 (2H, q, $J=7.3$ Hz), 1.37 (3H, t, $J=7.0$ Hz), 1.32 (18H, s)

Anal. Calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_2$, C: 78.14%, H: 8.84%, N: 3.96%; Found C: 78.33%, H: 8.94%, N: 3.69%.

上記アミノ体 (VIII-2) 101 mgをDMF (2 ml)に溶かし、DMF (2 ml) に懸濁させたNaH 90 mg を加えた。その後ヨウ化エチル (1 ml) を加え、室温で攪拌した。

TLC で原料消失を確認した後、反応液を水 (30 ml) にあけ塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー (n-ヘキサン : 酢酸エチル = 10 : 1) にて精製し、4-[N- エチル-N-(3, 5-ジ-tert-ブチルフェニル) アミノ] 安息香酸エチルエステル (99%) を得た。

Colorless powder (n-ヘキサン); mp 90 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.83 (2H, dd, $J=2.2, 9.2$ Hz), 7.31 (1H, t, $J=1.8$ Hz), 7.02 (2H, d, $J=1.5$ Hz), 6.64 (2H, dd, $J=2.2, 9.2$ Hz), 4.31 (2H, q, $J=7.0$ Hz), 3.79 (2H, q, $J=7.0$ Hz), 1.35 (3H, t, $J=7.0$ Hz), 1.32 (18H, s), 1.26 (3H, t, $J=7.0$ Hz)

Anal. Calcd for $\text{C}_{25}\text{H}_{35}\text{NO}_2$, C: 78.69%, H: 9.25%, N: 3.67%; Found C: 78.77%, H: 9.09%, N: 3.69%.

上記エステル体 (89 mg) をエタノール (4 ml) に溶かし、20% KOH 水溶液 (1 ml) を加えて還流した。原料消失後、反応液を 1 N 塩酸 (30 ml) にあけ、塩化メチレンで抽出した。有機層を硫酸マグネシウムで脱水し、溶媒を留去して DA212 を 80 mg (97%) 得た。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 225 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.88 (2H, dd, $J=2.2, 9.2$ Hz), 7.33 (1H, t, $J=1.8$ Hz), 7.02 (2H, d, $J=1.8$ Hz), 6.63 (2H, dd, $J=1.8, 8.8$ Hz), 3.80 (2H, q, $J=7.0$ Hz), 1.32 (18H, s), 1.27 (3H, t, $J=7.0$ Hz)

Anal Calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_2$, C: 78.14%, H: 8.84%, N: 3.96%; Found C: 78.20%, H: 8.91%, N: 3.92%.

例50 : 4-[N-n- プロピル-N-(3, 5-ジ-tert-ブチルフェニル) アミノ] 安息香酸エチルエステル (DA213) の製造

化合物VIII-2とヨウ化n-プロピルを用いて、例49の方法に従ってDA213 を合成した。

Colorless prisms (n-ヘキサン- 塩化メチレン); mp 247-248 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.87 (2H, dd, $J=2.2, 9.2$ Hz), 7.33 (1H, t, $J=1.8$

Hz), 7.03 (2H, d, J=1.8 Hz), 6.61 (2H, dd, J=1.8, 9.2 Hz), 3.66 (2H, t, J=7.7 Hz), 1.74 (2H, hex, J=7.7 Hz), 1.32 (18 H, s), 0.95 (3H, t, J=7.7 Hz).

Anal. Calcd for $C_{24}H_{33}NO_2$, C: 78.43%, H: 9.05%, N: 3.81%; Found C: 78.55%, H: 8.94%, N: 3.59%.

例51: 4-[N-フェニル-N-[2-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフチル)]アミノ]安息香酸(TA001)の製造

4-[N-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン-2-イル)アミノ]安息香酸エチルエステル(VI-2) 107 mg、ヨウ化フェニル 0.1 ml 及び tert-BuONa 33.5 mg を無水トルエン 5 ml に溶かし、アルゴン置換下、トリス(ジベンジリデンアセトン)ジパラジウム(0) 21 mg、BINAP (登録商標) 43 mg を加え、80℃で加熱した。1時間40分後、tert-BuONa 33 mg を追加した。更に1時間50分後、室温まで冷まし、水 30 ml にあけ塩化メチレンで抽出した。有機層を硫酸ナトリウムで脱水、濃縮後、フラッシュシリカゲルカラムクロマトグラフィー(n-ヘキサン:酢酸エチル=40:1)により精製して、4-[N-フェニル-N-[2-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフチル)]アミノ]安息香酸エチルエステル 28 mg (y. 22 %) を得た。

1H -NMR (400 MHz, $CDCl_3$) 7.84 (2H, dd, J=1.8, 8.8 Hz), 7.29 (2H, t, J=7.3 Hz), 7.19 (1H, d, J=8.4 Hz), 7.08-7.16 (4H, m), 6.97 (2H, dd, J=1.8, 8.8 Hz), 6.82 (1H, dd, J=2.6, 8.4 Hz), 4.33 (2H, q, J=7.3 Hz), 1.67 (4H, s), 1.36 (3H, t, J=7.3 Hz), 1.28 (6H, s), 1.17 (6H, s).

上記エステル体 23 mg をエタノール 3 ml に溶かし、20 % KOH 水溶液 0.5 ml を加え1時間還流した。反応液を 1N 塩酸にあけ塩化メチレンで抽出した。有機層を無水硫酸ナトリウムで脱水し、溶媒留去して黄白色結晶を 21 mg (定量的) 得た。得られた結晶を活性炭処理したのち、再結晶により白色結晶を得た。

TA001: colorless prism (n-ヘキサン-塩化メチレン); mp 239 °C

1H -NMR (400 MHz, $CDCl_3$) 7.88 (2H, dd, J=1.8, 8.8 Hz), 7.31 (2H, t, J=8.4

Hz), 7.22 (1H, d, J=8.4 Hz), 7.17 (2H, dd, J=1.5, 8.8 Hz), 7.12 (1H, t, J=7.3 Hz), 7.10 (1H, d, J=2.6 Hz), 6.97 (2H, dd, J=2.2, 9.2 Hz), 6.84 (2H, dd, J=2.6, 8.4 Hz), 1.68 (4H, s), 1.28 (6H, s), 1.18 (6H, s).

例52: 4-[N,N-ビス[2-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフチル)]アミノ]安息香酸(TA012)の製造

窒素雰囲気下、p-アミノ安息香酸エチルエステル (7.42 g)、2-ブromo-5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン (10 g)、炭酸カリウム (10.4 g)、酸化銅 (0.5 g)、ニトロベンゼン (5 ml) の混合物を約220 °Cで5時間攪拌した。反応混合物を冷却した後、エーテルを加えてろ過した。エーテル相を水洗し、減圧下に溶媒を留去し、残査をシリカゲルカラムクロマトグラフィー (n-ヘキサン:酢酸エチル= 1:5) により精製して、化合物VI-2 (3.5 g)と4-[N,N-ビス[2-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフチル)]アミノ]安息香酸エチルエステル (3.1 g)を得た。

ビス体: $^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.82 (2H, d, J=9 Hz), 7.19 (2H, d, J=8 Hz), 7.08 (2H, d, J=2 Hz), 6.94 (2H, d, J=9 Hz), 6.84 (2H, dd, J=8, 2 Hz), 4.32 (2H, q), 1.67 (8H, s), 1.35 (3H, t), 1.27 (12H, s), 1.17 (12H, s).

4-[N,N-ビス[2-(5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフチル)]アミノ]安息香酸エチルエステル (3 g)のエタノール (20 ml)溶液に水酸化ナトリウム (0.67 g) の水溶液 (3 ml) を加え、50°Cで3時間攪拌した。反応混合物を減圧濃縮した。残査に水を加え、0 °Cに冷却しながら塩酸水溶液を加えて中和した。混合物を酢酸エチルで抽出し、得られた残査をカラムクロマトグラフィー (酢酸エチル) で精製して、TA012 (1.5 g) を得た。

$^1\text{H-NMR}$ (400 MHz, CDCl_3) 7.87 (2H, d, J=9 Hz), 7.21 (2H, d, J=8 Hz), 7.10 (2H, d, J=2 Hz), 6.93 (2H, d, J=9 Hz), 6.86 (2H, dd, J=8, 2 Hz), 1.67 (8H, s), 1.27 (12H, s), 1.18 (12H, s).

試験例：HL-60 細胞における細胞分化誘導検定

各化合物に関して、単独での細胞分化誘導作用および共存するレチノイドの細胞分化誘導作用に対する効果を検討した。比較および共存させるレチノイドとしてレチノイン酸若しくはAm80 [4-[(5, 6, 7, 8-テトラヒドロ-5, 5, 8, 8- テトラメチル-2- ナフタレニル) カルバモイル] 安息香酸を用いた。特開昭61-76440号公報に記載された方法に準じて、前骨髄球性白血病細胞株HL-60 を用いて、顆粒球系への分化を形態変化およびニトロブルーテトラゾリウム(NBT) の還元能測定により判定した。表1には、各化合物単独の濃度依存的分化誘導能、及び $1 \times 10^{-9} \text{M}$ のレチノイン酸(RA)又はAm80の分化誘導能に対する濃度依存的効果を示し、表2には $1 \times 10^{-10} \text{M}$ Am80 の分化誘導能に対する各化合物の濃度依存的効果を示し、表3には、各化合物単独の濃度依存的分化誘導能及び $1 \times 10^{-10} \text{M}$ Am80 の分化誘導能に対する濃度依存的効果を示した。なお、以下の各表に示した分化した細胞の割合(%) はNBT還元能から算出したものであり、濃度は対数値で示し、-は未測定を意味する。

表 1

化合物	化合物単独での 分化誘導した細胞 の割合 (%)			$1 \times 10^{-9} \text{M}$ Am80 と共存 時の分化誘導した細胞 の割合 (%)				$1 \times 10^{-9} \text{M}$ RA と共存 時の分化誘導した 細胞の割合 (%)		
	濃 度	濃 度	濃 度	濃 度	濃 度	濃 度	濃 度	濃 度	濃 度	濃 度
	-8	-7	-6	なし	-8	-7	-6	なし	-8	-7
DM010	1	0	-	66	76	89	-	14	26	66
DM012	0	1	1	66	73	85	94	14	57	69
DM030	1	1	4	66	68	94	90	14	58	73
DM032	1	1	17	66	58	90	88	14	-	-

表 2

1×10^{-10} M Am80 と共存した場合の
分化誘導した細胞の割合 (%)

化合物	濃 度					
	なし	-10	-9	-8	-7	-6
DM021	4.5	-	6	12	43	83
DM030	15.5	38	41	43	81	90
DM031	4.5	8	14	41	81	86
DM032	15.5	36	39	46	81	87

表 3

化合物単独での分化誘導した細胞の割合 (%)					1×10^{-10} M Am80 と共存した場合 分化誘導した細胞の割合 (%)					
化合物	濃 度				濃 度					
	-9	-8	-7	-6	なし	-10	-9	-8	-7	-6
DA010	1.7	2.7	3.2	61	12	-	34	38	46	89
DA011	2.4	3.6	5	81	12	-	43	49	85	91
DA012	-	1.3	6.7	15.2	4.5	10	21	80	89	-
DA013	-	1	4	3.3	4.5	18	28	87	90	-
DA014	-	2.1	4.5	3.2	14	-	36	69	92	57
DA015	-	2.3	2.6	2.3	14	-	28	50	65	47
DA021	-	3.4	2.5	8.2	4.5	8.1	9.6	42	90	-
DA022	-	2.8	3.8	5.5	5.5	42	55	89	-	-
DA023	-	2	3.9	6.8	5.5	39	67	95	-	-
DA024	-	4.3	8.3	6.6	5.5	24	48	87	-	-
DA030	-	0.9	2.7	1.6	4	12	55	87	86	47
DA051	-	2.5	3.3	3	14	-	31	32	46	74
DA112	-	3.5	5	4	5.5	40	71	90	-	-
DA113	-	2.1	2.2	4.3	5.5	37	80	94	-	-
DA212	-	1.5	1.8	2.5	4.5	4.8	8.5	8	45	66
DA213	-	1.3	0.6	0.9	4.5	8	17	74	88	66

試験例2：糖尿病モデルマウスに対する血糖値降下作用

4～5 ヶ月齢の糖尿病を発症したKKマウスの尾静脈より血液を採取し、その血糖値を測定した。次に、各群のマウスの血糖値の平均が同じになるようにマウスを群わけし（一群、四匹）、被験物質を0.01～0.03% 含むように調製したマウス用粉末飼料(F-1、船橋農場)を各群のマウスに3日間与えた。対照として薬物を含まない粉末飼料を対照マウスに投与した。3日後にマウス尾静脈より血液を採取し、遠心分離により得られた血漿中のグルコース濃度をグルコースアナライザー、グルコローダー F (A & T社)にて測定した。被験物質の血糖降下率は以下の式により求めた。血糖降下率(%) = (対照マウスの血糖値 - 薬物投与マウスの血糖値) / 対照マウスの血糖値

表 4

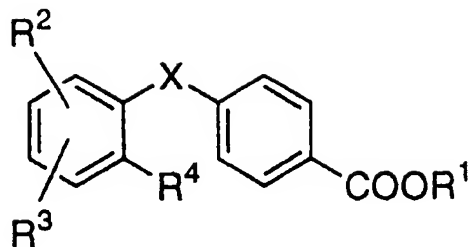
化合物	飼料中の濃度(%)	血糖値 (平均値)	血糖降下率(%)
対照		455 ± 10	
DA011	0.03	383 ± 38	15.9
DA051	0.03	462 ± 38	-1.4
DM010	0.03	431 ± 14	5.4
DM011	0.03	396 ± 44	13.1
DM030	0.03	416 ± 17	8.7
DM031	0.03	326 ± 30	28.3
対照		452 ± 38	
DA012	0.01	282 ± 47	37.6
DA012	0.03	352 ± 61	22.2
DA013	0.01	426 ± 53	5.9
DA013	0.03	430 ± 25	4.9
対照		374 ± 51	
DA012	0.03	255 ± 26	31.7

産業上の利用可能性

本発明の化合物は、レチノイン酸などのレチノイドの生理活性発現を調節する作用を有しているので、レチノイド作用調節剤などの医薬の有効成分として有用である。

請 求 の 範 囲

1. 下記の一般式(I):



〔式中、 R^1 は水素原子又は C_{1-6} アルキル基を示し； R^2 、 R^3 、及び R^4 はそれぞれ独立に水素原子、 C_{1-6} アルキル基、若しくは C_{1-6} アルコキシ基を示すか、又は R^2 及び R^3 が隣接する場合にはそれらは一緒になって R^2 及び R^3 が結合するフェニル基上の炭素原子とともに5ないし6員環を形成してもよく（上記の環はその環上に1個または2個以上の C_{1-4} アルキル基を有するか、1個または2個以上の置換基を有することもある1個の縮合ベンゼン環を有していてもよい）；Xは $-C(R^5)(R^6)-$ 又は $-NR^7-$ で表される二価の基を示す（式中、 R^5 は水素原子又は水酸基を示し； R^6 は置換基を有することもあるフェニル基、又は置換基を有することもある5ないし6員の飽和若しくは不飽和の含窒素ヘテロ環基を示し； R^7 は水素原子、1個又は2個以上の不飽和結合を有することもある C_{1-12} アルキル基、 C_{3-12} シクロアルキル基、 C_{4-12} シクロアルキル置換アルキル基、置換基を有することもあるアラシル基、 C_{1-12} アルカノイル基、置換基を有することもあるアロイル基、又は置換基を有することもあるフェニル基を示す）〕で表される化合物またはその塩。

2. 請求の範囲第1項に記載の化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質を有効成分として含む医薬。

3. レチノイド作用調節剤である請求の範囲第2項に記載の医薬。

4. 核内レセプター・スーパーファミリーに属する核内レセプターに結合して生理作用を発揮する生理活性物質の作用増強剤又は作用抑制剤として用いる請求の範囲第2項又は第3項に記載の医薬。

5. 該生理活性物質がレチノイドである請求の範囲第4項に記載の医薬。
6. 請求の範囲第1項に記載の化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質とレチノイドを含む医薬用組成物。
7. 請求の範囲第2ないし5項のいずれか1項に記載の医薬の製造のための請求の範囲第1項に記載の化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質の使用。
8. 哺乳類動物の生体内においてレチノイドの作用を調節する方法であって、請求の範囲第1項に記載の化合物及び生理学的に許容されるその塩、並びにそれらの水和物及びそれらの溶媒和物からなる群から選ばれる物質の有効量をヒトを含む哺乳類動物に投与する工程を含む方法。
9. ビタミンA欠乏症、皮膚疾患、アレルギー疾患、免疫性疾患、骨疾患、アルツハイマー病、ハンチントン舞蹈病、又は悪性腫瘍の予防及び／又は治療方法である請求の範囲第8項に記載の方法。
10. 糖尿病、動脈硬化症、高脂血症、又は高コレステロール血症の予防及び／又は治療方法である請求の範囲第8項に記載の方法。

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01211

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl⁶ C07C63/49, C07C65/24, C07C229/54, C07C229/62, C07C233/65,
C07C233/81, C07D249/08, C07D257/04, C07D233/56, C07D295/08,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁶ C07C1/00-C07C409/44, C07D201/00-521/00, A61K6/00-49/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO, 97/48397, A1 (KLINGE PHARMA GMBH & CO KG), December 24, 1997 (24. 12. 97) & DE, 19624668, A1 & AU, 9732624, B	1, 2, 7
P, A		3-6
P, X	WO, 97/34589, A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE), September 25, 1997 (25. 09. 97) & AU, 9725388, B & DE, 19624668, A1	1, 2, 7
P, A		3-6
X	JP, 8-169857, A (CIRD Galderma), July 2, 1996 (02. 07. 96) & FR, 2719043, A1 & EP, 679630, A1 & CA, 2147807, A1	1, 2, 7
A		3-6

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
--	---

Date of the actual completion of the international search
June 16, 1998 (16. 06. 98)

Date of mailing of the international search report
June 30, 1998 (30. 06. 98)

Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01211

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 55-9089, A (The Dow Chemical Co.), January 22, 1980 (22. 01. 80)	1, 2, 7
A	& US, 4143151, A & GB, 2024011, A1 & DE, 2926644, A1 & FR, 2430232, A1	3-6
X	US, 5612474, A (ELI LILLY AND COMPANY), May 18, 1997 (18. 05. 97) (Family: none)	1, 2, 7
A		3-6
X	PATEL, V.F. et al., "Novel acid labile COL1 trityl-linked difluoronucleoside immunoconjugates: synthesis, characterization", Bioconjugate Chem., (1996) 7(4) p.497-510	1, 2, 7
A		3-6
X	WO, 96/36620, A1 (SMITHKLINE BEECHAM S P A), November 21, 1996 (21. 11. 96)	1, 2, 7
A	& AU, 9658998, B & EP, 825991, A1	3-6
X	WO, 96/34604, A1 (SANDOZ LTD), November 7, 1996 (07. 11. 96)	1, 2, 7
A	& AU, 9656368, B	3-6
X	US, 5576460, A (MASSACHUSETTS INST TECH), November 19, 1996 (19. 11. 96) (Family: none)	1, 2, 7
A		3-6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01211

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-10

because they relate to subject matter not required to be searched by this Authority, namely:

The subject matters of the above claims involve inventions pertaining to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required to search.

2. ☐ Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01211

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

C07D295/14, A61K31/415, A61K31/41, A61K31/39, C07D31/395, A61K31/445,
A61K31/40, A61K31/535

国際調査報告

国際出願番号 PCT/J P 98/01211

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl^o C07C63/49, C07C65/24, C07C229/54, C07C229/62, C07C233/65, C07C233/81, C07D249/08, C07D257/04, C07D233/56, C07D295/08, C07D295/14, A61K31/415, A61K31/41, A61K31/39, C07D31/395, A61K31/445, A61K31/40, A61K31/535

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl^o C07C1/00-C07C409/44, C07D201/00-521/00, A61K6/00-49/04

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース (データベースの名称、調査に使用した用語)

CAS ONLINE

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
P, X	WO, 97/48397, A1 (KLINGE PHARMA GMBH & CO KG) 24. 12月. 1997	1, 2, 7
P, A	(24. 12. 97) & DE, 19624668, A1 & AU, 9732624, B	3-6
P, X	WO, 97/34589, A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE)	1, 2, 7
P, A	25. 9月. 1997 (25. 09. 97) & AU, 9725388, B & DE, 19624668, A1	3-6

☒ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

* 引用文献のカテゴリー

「A」 特に関連のある文献ではなく、一般的技術水準を示すもの

「E」 先行文献ではあるが、国際出願日以後に公表されたもの

「L」 優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)

「O」 口頭による開示、使用、展示等に言及する文献

「P」 国際出願日前で、かつ優先権の主張の基礎となる出願

の日の後に公表された文献

「T」 国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」 特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」 特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&」 同一パテントファミリー文献

国際調査を完了した日

16. 06. 98

国際調査報告の発送日

30.06.98

国際調査機関の名称及びあて先

日本国特許庁 (ISA/J P)

郵便番号100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

大久保 元 浩

4H

8828

電話番号 03-3581-1101 内線 3445

第Ⅰ欄 請求の範囲の一部の調査ができないときの意見（第1ページの1の続き）

法第8条第3項（PCT17条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1. ☒ 請求の範囲 8-10 は、この国際調査機関が調査をすることを要しない対象に係るものである。つまり、

上記請求の範囲は、治療による人体の処置方法に係る発明を包含しているから、この国際調査機関が国際出願について国際調査を行うことを要しない対象に係るものである。

2. ☐ 請求の範囲 _____ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

3. ☐ 請求の範囲 _____ は、従属請求の範囲であってPCT規則6.4(a)の第2文及び第3文の規定に従って記載されていない。

第Ⅱ欄 発明の単一性が欠如しているときの意見（第1ページの2の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1. ☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。
2. ☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。
3. ☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったため、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。
4. ☐ 出願人が必要な追加調査手数料を期間内に納付しなかったため、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

- ☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
- ☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。

C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X A	JP, 8-169857, A (セ・イ・エル・デ・カルテルマ) 2. 7月. 1996 (02. 07. 96) & FR, 2719043, A1 & EP, 679630, A1 & CA, 2147807, A1	1, 2, 7 3-6
X A	JP, 55-9089, A (サ・タ・ウ・ケミカル・カンパニー) 22. 1月. 1980 (22. 01. 80) & US, 4143151 A & GB, 2024011, A1 & DE, 2926644, A1 & FR, 2430232 , A1	1, 2, 7 3-6
X A	US, 5612474, A (ELI LILLY AND COMPANY) 18. 5月. 1997 (18. 05. 97) (ファミリーなし)	1, 2, 7 3-6
X A	PATEL, V. F. et al. 'Novel acid labile COL1 trityl-linked difluoronucleoside immunoconjugates: synthesis, character- ization', Bioconjugate Chem., (1996) 7(4) p. 497-510	1, 2, 7 3-6
X A	WO, 96/36620, A1 (SMITHKLINE BEECHAM S P A) 21. 11月. 96 (21. 11. 96) & AU, 9658998, B & EP, 825991, A1	1, 2, 7 3-6
X A	WO, 96/34604, A1 (SANDOZ LTD) 7. 11月. 96 (07. 11. 96) & AU, 9656368, B	1, 2, 7 3-6
X A	US, 5576460, A (MASSACHUSETTS INST TECH) 19. 11月. 1996 (19. 11. 96) (ファミリーなし)	1, 2, 7 3-6